IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

WYETH, Plaintiff, v. IMPAX LABORATORIES, INC., Defendant.	Civil Action No.: 06-222 JJF **PUBLIC VERSION**

DECLARATION OF MARY B. MATTERER IN SUPPORT OF DEFENDANT'S OPENING CLAIM CONSTRUCTION BRIEF

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IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

WYETH, Plaintiff,	
v.	Civil Action No.: 06-222 JJF
IMPAX LABORATORIES, INC., Defendant.	**FILED UNDER SEAL**

DECLARATION OF MARY B. MATTERER IN SUPPORT OF DEFENDANT'S OPENING CLAIM CONSTRUCTION BRIEF

I, Mary B. Matterer, declare:

1. I am an attorney licensed to practice law in the State of Delaware and am a partner in the law firm of Morris James LLP, 500 Delaware Avenue, Suite 1500, Wilmington, Delaware 19801-1494, counsel for Defendant Impax Laboratories, Inc. in the above-captioned action. I am duly admitted to practice law before this Court. Except where expressly stated, I have knowledge of the facts set forth herein, and if called to testify as a witness thereto, could do so competently under oath.

2. Attached hereto as Exhibit A is a true and correct copy of a chart titled "Comparison of Claim Constructions" which sets forth the parties' respective constructions of the disputed claims.

3. Attached hereto as Exhibit B is a true and correct copy of the Markman Opinion issued on September 6, 2005 in *Wyeth v. Teva Pharmaceuticals USA, Inc.*, United States District Court for the District of New Jersey, Case No. 2:03-CV-1293.

4. Attached hereto as Exhibit C is a true and correct copy of U.S. Patent Number 6,274,171 B1.

5. Attached hereto as Exhibit D is a true and correct copy of U.S. Patent Number 4,535,186.

6. Attached hereto as Exhibit E is a true and correct copy of a Certificate Extending Patent Term Under 35 U.S.C. § 156 for U.S. Patent Number 4,535,186 issued by the United States Patent & Trademark Office on April 25, 1996.

7. Attached hereto as Exhibit F are relevant excerpts from the transcript of John Clark's deposition which was taken on November 4, 2004 in *Wyeth v. Teva Pharmaceuticals USA, Inc.*, United States District Court for the District of New Jersey, Case No. 2:03-CV-1293.

8. Attached hereto as Exhibit G is a true and correct copy of an excerpt from the file history of U.S. Patent Application Number 08/821,137 titled "Extended Release Formulation," dated March 20, 1997.

9. Attached hereto as Exhibit H is a true and correct copy of an excerpt from the file history of U.S. Patent Application Number 08/821,137 titled "Interview Summary," dated August 5, 1997.

10. Attached hereto as Exhibit I is a true and correct copy of U.S. Patent Number 5,506,270.

11. Attached hereto as Exhibit J is a true and correct copy of an excerpt from the file history of U.S. Patent Application Number 08/821,137 titled "Notice of Abandonment," dated February 3, 1998.

12. Attached hereto as Exhibit K is a true and correct copy of an excerpt from the file history of U.S. Patent Application Number 08/964,328 titled "Office Action Summary."

13. Attached hereto as Exhibit L is a true and correct copy of an excerpt from the file history of U.S. Patent Application Number 08/964,328 titled "Extended Release Formulation."

14. Attached hereto as Exhibit M is a true and correct copy of U.S. Patent Number 6,696,496.

15. Attached hereto as Exhibit N is a true and correct copy of an excerpt from *Handbook of Pharmaceutical Granulation Technology*, Second Edition (2005).

16. Attached hereto as Exhibit O is a true and correct copy of an excerpt from *Webster's Third New International Dictionary* (2002).

17. Attached hereto as Exhibit P is a true and correct copy of an excerpt of Wyeth's Opening Claim Construction Brief in *Wyeth v. Teva Pharmaceuticals USA, Inc.*, United States District Court for the District of New Jersey, Case No. 2:03-CV-1293.

I declare under penalty of perjury under the laws of the state of Delaware that the foregoing is true and correct to the best of my knowledge.

Executed this 8th day of May, 2007 at Wilmington, Delaware.

MARY B. MATTERER

EXHIBIT A

Wyeth v. Impax Laboratories

COMPARISON OF PROPOSED CLAIM CONSTRUCTIONS

Impax Claim Term	Impax's Construction	Wyeth Claim Term	Wyeth's Construction
with diminished incidence(s) of nausea and emesis	a decrease in the number of patients suffering from nausea and vomiting compared to patients receiving the same total daily dose of an immediate release formulation that is administered at least twice a day	with diminished incidence(s) of nausea and emesis	The degree and/or frequency of nausea and emesis from the extended release formulation administered once-a-day is less than what would be experienced by patients receiving the same total daily dose of an immediate release formulation that is administered at least twice a day.
extended release formulation	a formulation comprising venlafaxine, microcrystalline cellulose, and, optionally, HPMC coated with a mixture of ethyl cellulose and HPMC in an amount needed to provide a specific unit dosage administered once-a-day to provide a therapeutic blood plasma level of venlafaxine over the entire 24-hour period of administration	extended release formulation	A formulation, other than a hydrogel tablet, which releases the active ingredient at a slower rate than the immediate release formulation of the active ingredient such that the dosing frequency is once-a-day rather than the plural daily dosing for the immediate release formulation.
for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride	the peak(s) and trough(s) due to the "therapeutic metabolism" of any second or third dose given in a single day is eliminated by dosing only once every 24 hours	A method for eliminating the troughs and peaks of drug concentration in a patients blood plasma attending the therapeutic metabolism of plural daily doses or venlafaxine hydrochloride	A method in which the extended release formulation is administered once in a 24-hour period, resulting in a venlafaxine blood plasma concentration that rises to a maximum value, followed by a generally protracted decrease over the remaining period while maintaining during that 24-hour period levels of venlafaxine in blood plasma that are sufficient to provide, during the course of treatment, relief from the condition being treated, thereby eliminating the multiple sharp peaks and troughs resulting from multiple daily dosing of the same total daily dose of the immediate release formulation as reflected in a graph of venlafaxine blood plasma concentration versus time.

EXHIBIT B

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

WYETH, **Plaintiff,** **v.** **TEVA PHARMACEUTICALS USA, INC. and TEVA PHARMACEUTICAL INDUSTRIES LTD.,** **Defendants.**	03-CV-1293 (WJM) MARKMAN OPINION

This matter comes before the Court on the parties' submissions seeking construction of four disputed claim terms found in the patents-in-suit. Having taken into consideration the parties' submissions and their arguments made during the *Markman* hearing, the Court construes the disputed claim terms as follows.

BACKGROUND

This is an Abbreviated New Drug Application ("ANDA") patent infringement action. Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries Ltd. ("Teva") filed an ANDA seeking to market a generic version of Wyeth's Effexor® XR. Wyeth filed suit, alleging Teva's generic extended release venlafaxine formulation infringes three of its patents: U.S. Patent Nos. 6,274,171 B1 (the "'171 patent"), 6,419,958 B2 (the "'958 patent"), and 6,403,120 B1 (the "'120 patent"). The three patents are related and share an essentially identical specification.

Wyeth charges Teva with infringement of claims 20-25 of the '171 patent, claims 1-6 of the '958 patent, and claims 1, 2, 13 and 14 of the '120 patent. These claims are all method claims and are directed towards a method of administering an extended release formulation of venlafaxine hydrochloride that provides a therapeutic blood plasma concentration of venlafaxine over twenty-four hours. The specification states that the extended release formulation provides two advantages over the immediate release formulation. First, it eliminates the sharp peaks and troughs in blood plasma drug levels caused by multiple daily dosing with conventional immediate release venlafaxine hydrochloride tablets. '171 patent, col. 2, lines 24-28.[1] Thus, rather than take two to three doses a day, patients need only take the extended release formulation once a day. Second, it reduces the side effects experienced by patients who have taken the immediate release tablets. *See id.* at col. 2, lines 46-55. The extended release formulation was found to reduce the incidence of nausea and emesis (the act of vomiting). According to Wyeth, these two advantages provided improved patient compliance and tolerability, making Effexor® XR a blockbuster drug. (*See* Wyeth's Br. at 2).

Although the named inventors attempted to develop an extended release formulation in the form of a tablet, they failed, finding it "impossible" to achieve a sustained release tablet formulation. Col. 10, lines 53-57. They did, however, succeed in developing a film-coated spheroid formulation that could be administered in a capsule. The specific formulation they found worked was composed of "venlafaxine hydrochloride, microcrystalline cellulose and,

[1]Because the patents-in-suit share an essentially identical specification, all future citations will be to the '171 patent unless otherwise noted.

optionally, hydroxypropylmethylcellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose." Col. 2, line 67 - col. 3, line 2.

Prior to submitting their *Markman* briefs, the Court required the parties to submit a Joint Claim Construction Chart ("Chart") setting forth the claim terms in dispute and the parties' respective proposed constructions for each term. The parties identified four disputed claim terms: "extended release formulations," "spheroid," "with diminished incidence(s) of nausea and emesis," and "encapsulated." (*See* Chart). For claim construction purposes, the following claims are illustrative of how these terms are used. Claims 20 and 21 of the '171 patent recite:

> 20. A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty four hour period with diminished incidences of nausea and emesis which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about four to about eight hours, said formulation containing venlafaxine hydrochloride as the active ingredient.
>
> 21. A method for eliminating the troughs and peaks of drug concentration in a patients [sic] blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about four to about eight hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

Claims 1 and 14 of the '120 patent recite:

> 1. A method for providing therapeutic blood plasma concentration of venlafaxine over a twenty four hour period with diminished incidence of nausea and emesis which comprises administering orally to a patient in need thereof, an extended release formulation that provides peak blood plasma levels of venlafaxine of no more than about 150 ng/ml, said formulation containing venlafaxine hydrochloride as the active ingredient.
>
> 13. The method of claim 1 wherein the extended release formulation comprises venlafaxine hydrochloride in an encapsulated spheroid.

DISCUSSION

I. Law of Claim Construction

The Federal Circuit en banc recently reaffirmed the claim construction methodology articulated by *Markman v. Westview Instruments, Inc.*[2] and its progeny and clarified the role that dictionaries play in claim construction. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (en banc). In *Phillips*, the Federal Circuit reestablished the primacy of the intrinsic evidence – the claims, specification and prosecution history – and reclassified dictionaries as part of the less significant extrinsic evidence. In doing so, the Federal Circuit emphasized the need to construe the claims in their proper context, which is the specification. *Id.* at 1321.

The objective of claim construction is to determine how a person of ordinary skill in the art would understand the claim terms. *Id.* at 1313, 1324. Generally, claim terms are given their ordinary and customary meaning. *Id.* at 1312-13 (quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)). That meaning "is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." *Id.* at 1313. In determining the ordinary meaning of claim terms, the person of ordinary skill in the art is deemed to read the claim terms in the context of the entire patent, including the particular claims in which they appear and the specification. *Id.* at 1313.

The claims "provide substantial guidance as to the meaning of particular claim terms." *Id.* at 1314. Oftentimes, the context in which a term is used in asserted and unasserted claims

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[2] 52 F.3d 967 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996).

"can be highly instructive." *Id.* Further, differences among claims can provide useful insight into a term's meaning. *Id.*

But the claims cannot be looked at in isolation; rather, they must be considered in view of the specification. *Id.* at 1315. The specification is considered to be the "single best guide" for construing the claims. *Id.* The specification may reveal whether the patentee acted as his own lexicographer by giving a claim term a special definition. *Id.* Or, it may show that the patentee intentionally disclaimed claim scope. *Id.* In either case, the patentee's intent is dispositive. *Id.*

A court should also consider the prosecution history, if it is in evidence. *Id.* at 1317. The prosecution history "consists of the complete record of the proceedings before the [Patent and Trademark Office ("PTO")] and includes the prior art cited during the examination of the patent." *Id.* (citing *Autogiro Co. of Am. v. United States*, 181 Ct. Cl. 55, 384 F.2d 391, 399 (1967)). Although it "often lacks the clarity of the specification and thus is less useful for claim construction purposes," the prosecution history sheds light on the PTO's and inventor's understanding of the patent. *Id.*

A court may, in its discretion, consult extrinsic evidence, i.e., dictionaries, treatises, and expert and inventor testimony, when construing claim terms. *Id.* A court may consult extrinsic evidence to educate itself about the field of the invention and to aid its understanding of what one of ordinary skill in the art would understand a claim term to mean. *Id.* at 1319. But extrinsic evidence is "less significant" and "less reliable" than intrinsic evidence because it gives meaning to a claim term in the abstract, rather than in the particular context of the patent. *Id.* at 1317-18. Thus, although it may play a supporting role in claim construction, extrinsic evidence may not be used to contradict an unambiguous meaning established by the intrinsic record. *See id.* at 1324.

II. The Disputed Claim Terms

1. "extended release formulation"

Wyeth contends that "extended release formulation" should be given its ordinary meaning and construed as "[a] formulation which releases the active ingredient at a slower rate than the immediate release formulation of the active ingredient such that the dosing frequency is once-a-day rather than the plural daily dosing for the immediate release formulation." (Chart). Teva asserts that the patentees acted as their own lexicographers by identifying certain ingredients that must be present in the formulation. Teva asserts that "extended release formulation" means "[a] formulation comprising venlafaxine hydrochloride, microcrystalline cellulose and, optionally, hydroxypropylmethylcellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose in an amount needed to provide a specific unit dosage administered once-a-day to provide a therapeutic blood plasma level of venlafaxine over the entire 24-hour period of administration." (*Id.*, emphasis added). Because the Court agrees with Teva that the patentees acted as their own lexicographers, the Court will adopt Teva's proposed claim construction.

The Court begins by looking at the context in which the term "extended release formulation" is used in the claims of the patents-in-suit. Wyeth argues that the asserted claims demonstrate that the patentees did not intend to limit "extended release formulation" to any specific set of ingredients. Every asserted claim recites: "A method . . . which comprises administering orally to a patient in need thereof, an . . . extended release formulation . . ., said formulation containing venlafaxine hydrochloride as the active ingredient." (*See, e.g.*, '171 patent, claim 20, emphasis added). Wyeth argues that if in fact "extended release formulation"

encompassed particular ingredients, including venlafaxine hydrochloride, then the limitation "said formulation containing venlafaxine hydrochloride as the active ingredient" would be superfluous. (Wyeth's Br. at 11). According to Wyeth, if "extended release formulation" already included venlafaxine hydrochloride, then there is no need for the claims to specify the active ingredient. Thus, argues Wyeth, "extended release formulation" does not include any particular ingredients.

Wyeth also contends that the doctrine of claim differentiation supports its broad construction of "extended release formulation." The doctrine of claim differentiation gives rise to a presumption that a limitation added in a dependent claim is not present in the independent claim. *Phillips*, 415 F.3d at 1314-15. Comparing independent claim 1 of the '120 patent with dependent claim 3, Wyeth argues that the doctrine creates a presumption that "extended release formulation" does not include specific ingredients. (Wyeth's Br. at 13). Independent claim 1 recites: "A method . . . which comprises administering orally to a patient in need thereof, an extended release formulation . . ., said formulation containing venlafaxine hydrochloride as the active ingredient." '120 patent, claim 1 (emphasis added). Dependent claim 3 recites: "The method of claim 1 wherein the extended release formulation comprises venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and optionally, hydroxypropylmethylcellulose." '120 patent, claim 3 (emphasis added). Because claim 3 includes the additional limitation of specific ingredients, the Court agrees with Wyeth that a presumption arises that claim 1 does not include that limitation. Thus, the Court agrees with Wyeth that the plain language of the claims implies that "extended release formulation" does not include specific ingredients.

Teva does not dispute that the claims, on their face, imply a broad construction for "extended release formulation." Rather, Teva argues that the presumption the broader construction applies is overcome by the narrow definition given to "extended release formulation" by the patentees in the specification. This Court agrees.

The patentees defined "extended release formulation" several times in the specification. In the abstract, they disclosed:

> More particularly, the invention comprises an extended release formulation of venlafaxine hydrochloride comprising a therapeutically effective amount of venlafaxine hydrochloride in spheroids comprised of venlfaxine hydrochloride, microcrystalline cellulose and, optionally, hydroxypropylmethylcellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose.

'171 patent, Abstract. They reiterated this same restrictive definition in the "Brief Description of the Invention:"

> The formulations of this invention comprise an extended release formulation of venlafaxine hydrochloride comprising a therapeutically effective amount of venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and, optionally, hydroxypropylmethylcellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose.

'171 patent, col. 2, line 62 - col. 3, line 2. Only after setting forth this description of their invention, did the inventors then go on to address the preferred embodiments of their invention. *See* '171 patent, col. 3, lines 5-62. Similarly, in the "Detailed Description of the Invention," the patentees defined "extended release formulations" by their ingredients:

> The extended release formulations of this invention are comprised of [venlafaxine] hydrochloride in admixture with microcrystalline cellulose and hydroxypropylmethylcellulose. Formed as beads or

> spheroids, the drug containing formulation is coated with a mixture of ethyl cellulose and hydroxypropylmethyl cellulose [sic] to provide the desired level of coating . . . .

'171 patent, col. 4, lines 9-15 (emphasis added).

Wyeth asserts that these statements merely identify a preferred embodiment of the invention. The Court disagrees. Because the specification definitively states that the "extended release formulations" of the invention are limited to particular ingredients, the Court finds that the patentees acted as their own lexicographers and limited the meaning of "extended release formulation." *See Astrazeneca AB v. Mutual Pharm. Co.*, 384 F.3d 1333, 1339-40 (Fed. Cir. 2004) (finding that the inventors acted as their own lexicographers and limited the term "solubilizer" to surfactants by stating in the specification that "[t]he solubilizers suitable according to the invention are defined below", and later describing the suitable solubilizers as surfactants).

Moreover, the specification provides additional support for a narrow construction of "extended release formulation." Although it is improper to limit the claims based on the preferred embodiments, the Federal Circuit has stated that the "preferred embodiments can shed light on the intended scope of the claims." *Id.* at 1340. Here, the specification sets forth seven examples describing different embodiments the named inventors worked with. Each and every embodiment of an "extended release formulation" recited in these examples includes venlafaxine hydrochloride, microcrystalline cellulose and, optionally, HPMC[3] coated with ethyl cellulose and HPMC. *See, e.g.*, '171 patent, col. 5, line 33 - col. 10, line 57. The fact that all of these examples use the same core set of ingredients buttresses the conclusion that "extended release

[3]"HPMC" is the abbreviation for "hydroxypropylmethylcellulose."

formulation" should be narrowly construed. *See Astrazeneca*, 384 F.3d at 1340-41 (finding additional support for a limited construction of "solubilizer" in the fact that "all of the solubilizers listed in the specification and used in the working examples were surfactants").

Further, the specification distinguishes the "extended release formulations" of the invention from extended release hydrogel tablet formulations. Wyeth admits that under its proposed construction, an extended release hydrogel tablet having the claimed *in vivo* characteristics may fall within the asserted claims. (*See* Wyeth's Br. at 16 n.6). The specification, however, discloses that the inventors' attempts to develop extended release hydrogel tablets were "fruitless" and teaches one of ordinary skill that it is "impossible to achieve" the desired dissolution rates using hydrogel tablet technology. Col. 4, lines 60-64; col. 10, lines 53-57. These statements were made without qualification. Accordingly, the specification supports construing "extended release formulation" more narrowly than Wyeth proposes. *See Cultor Corp. v. A.E. Staley Mfg. Co.*, 224 F.3d 1328, 1331 (Fed. Cir. 2000) ("Claims are not correctly construed to cover what was expressly disclaimed.").

Wyeth responds that the specification supports its broader, ordinary meaning of the term. Wyeth asserts that Teva ignores several portions of the specification which allegedly refer only to the "extended release formulation" as including venlafaxine hydrochloride. *See, e.g.*, '171 patent, Abstract ("This invention relates to a 24 hour extended release dosage formulation and unit dosage form thereof of venlafaxine hydrochloride, an antidepressant . . . .") (emphasis added); *Id.* at col. 2, lines 14-16 ("In accordance with this invention, there is provided an extended release (ER), encapsulated formulation containing venlafaxine hydrochloride as the active drug s [sic] component . . . .") (emphasis added); *Id.* at col. 2, lines 37-44 ("Hence, in

accordance with the use aspect of this invention, there is provided a method for moderating the plural blood plasma peaks and valleys . . . which comprises administering to a patient in need of treatment with venlafaxine hydrochloride, a one-a-day, extended release formulation of venlafaxine hydrochloride.") (emphasis added). Wyeth further asserts that its broad construction is supported by those portions of the specification that compare "extended release formulations" with immediate release formulations. *See, e.g.*, '171 patent, col. 2, lines 24-37 (contrasting blood plasma profiles for both types of formulations without reference to specific ingredients). And Wyeth contends that Table 1 in the specification supports a broader construction because it allegedly teaches an ordinary artisan how to screen for other useful inactive ingredients that may work in combination with venlafaxine hydrochloride to develop an extended release venlafaxine formulation. But there is no merit to Wyeth's arguments because they ignore those portions of the specification set forth above that explicitly characterize and limit the invention to a formulation containing specific ingredients.

When the term "extended release formulation" is looked at in its proper context in the specification, this Court believes that one of ordinary skill in the art would construe the term to include specific ingredients. The unequivocal language the patentees used when describing their invention – "the invention comprises an extended release formulation of", "[t]he formulations of this invention comprise" and "[t]he extended formulations of this invention are" – rebuts the presumption established by the doctrine of claim differentiation. *See, e.g., Kraft Foods, Inc. v. Int'l Trading Co.*, 203 F.3d 1362, 1368-69 (Fed. Cir. 2000) (finding the presumption of claim differentiation overcome because the specification and prosecution history described the "protecting back panel" as one that must be relatively stiff). Although this may make certain

dependent claims coterminous and certain claim limitations superfluous, that result is inevitable and inescapable in a case such as this where the patentees act as their own lexicographers. *See Multiform Desiccants, Inc. v. Medzam, Ltd.*, 133 F.3d 1473, 1480 (Fed. Cir. 1998) ("[T]he doctrine of claim differentiation can not broaden claims beyond their correct scope, determined in light of the specification and the prosecution history and any relevant extrinsic evidence."); *Sulé v. Kloehn Co., Ltd.*, 149 F. Supp. 2d 115, 128 (D.N.J. 2001) ("Claim differentiation is a guide, not a rigid rule. If a claim will bear only one interpretation, similarity will have to be tolerated.") (quoting *Autogiro*, 384 F.2d at 404).

The portions of the prosecution history in evidence do not alter this conclusion. Although Wyeth contends that the prosecution history supports a broader construction because the method claims were allowed without limitation to specific ingredients, given the clear and unambiguous language in the specification, the Court believes that the prosecution adds, at most, nothing more than the claims themselves reveal. That being the case, the definition provided by the specification, which is the "single best guide to the meaning of a disputed term," shall be adopted. *Vitronics*, 90 F.3d at 1582.

Because the meaning of the term can be ascertained from the intrinsic record, the Court will not rely on extrinsic evidence that suggests a broader construction. *See Phillips*, 415 F.3d at 1324 (prohibiting the use of extrinsic evidence to contradict the unambiguous meaning provided to a claim term by the intrinsic evidence). That evidence takes the term out of its all-important context in the specification and, thus, will be given no weight.

In sum, "extended release formulation" means "a formulation comprising venlafaxine hydrochloride, microcrystalline cellulose and, optionally, HPMC coated with a mixture of ethyl

cellulose and HPMC in an amount needed to provide a specific unit dosage administered once-a-day to provide a therapeutic blood plasma level of venlafaxine over the entire 24-hour period of administration."

2. "spheroid"

Wyeth contends that "spheroid" means "[o]ne or more particles that are generally shaped like a sphere, although they do not have to be perfectly round", including "granules, beads and pellets." (Chart). Teva asserts that "spheroid" means "[o]ne or more particles that are generally shaped like a sphere and result from an extrusion and spheronization process." (*Id.*, emphasis added). Essentially, although the parties agree that "spheroid" means "one or more particles that are generally shaped like a sphere," they dispute whether the term should be limited to a particular manufacturing process. Because the intrinsic evidence does not narrow the meaning of "spheroids," which connotes shape, the Court will not limit its construction to a specific manufacturing process.

The term "spheroid" is contained in asserted claims 13 and 14 of the '120 patent. Wyeth argues that these claims are drawn broadly to include any "spheroid," regardless of the method of manufacture. Claim 13 recites: "The method of claim 1 wherein the extended release formulation comprising venlafaxine hydrochloride in a spheroid." '120 patent, claim 13 (emphasis added). Claim 14 is similarly broad: "The method of claim 1 wherein the extended release formulation comprises venlafaxine hydrochloride in an encapsulated spheroid." '120 patent, claim 14 (emphasis added). Thus, the plain language of the claims does not suggest that the term "spheroid" has anything other than its ordinary meaning. Morever, the specification

uses the ordinary meaning of "spheroid," equating "beads" with "spheroids" without any apparent limitation on the method of manufacture. *See* '171 patent, col. 4, lines 12-13 ("Formed as beads or spheroids, the drug containing formulation is coated . . . ."). This ordinary, unrestricted meaning is consistent with how "spheroid" is defined in a dictionary – "[a] body that is shaped like a sphere but is not perfectly round, esp. an ellipsoid that is generated by revolving an ellipse around one of its axes." Am. Heritage College Dict. 1310 (3d ed. 1993).

Teva does not dispute that Wyeth's construction comports with the ordinary meaning of the word "spheroid." (*See* Teva's Opp'n Br. at 23). Rather, it contends that in this case the patents do not support the broader definition because they only identify one method of manufacture – the extrusion and spheronization process. For example, in the "Background of the Invention," the patentees described the process they used for making "spheroids:"

> In this situation, the extended release capsule dosage forms may be formulated by mixing the drug with one or more binding agents to form a uniform mixture which is then moistened with water or a solvent such as ethanol to form an extrudable plastic mass from which small diameter, typically 1 mm, cylinders of drug/matrix are extruded, broken into appropriate lengths and transformed into spheroids using standard spheronization equipment. The spheroids, after drying, may then be film-coated to retard dissolution.

'171 patent, col. 1, lines 38-47 (emphasis added); *see also* col. 5, lines 1-13 (stating that the addition of microcrystalline cellulose and HPMC made manufacture of spheroids with extruders possible); col. 6, lines 6-11 (stating that different extruders allowed spheroids to be made without HPMC).

Teva overreaches. Although the patents disclose only one method of manufacturing "spheroids" – the extrusion and spheronization process – it appears to be described as a preferred

method of manufacture, not the only method of manufacture. *See* '171 patent, col. 1, lines 38-47 (stating that the extended release formulations "may be formulated by" extrusion and spheronization, not must be formulated by this method). Teva appears to be attempting to import the preferred process into the claims. But there is no clear disclaimer of the term's ordinary meaning, nor do the patentees define "spheroid" as being limited to that method of manufacture. Further, the Federal Circuit has held that merely disclosing only one method of manufacture in the specification does not, by itself, limit the term to that one method. *See Vanguard Products Corp. v. Parker Hannifan Corp.*, 234 F.3d 1370, 1371-72 (Fed. Cir. 2000) (construing the word "integral" to define the relationship between layers in a gasket, and refusing to limit the formation of those layers by co-extrusion, the only manufacturing process disclosed in the specification and extolled in the prosecution history); *AFG Indus., Inc. v. Cardinal IG Co., Inc.*, 375 F.3d 1367, 1373 (Fed. Cir. 2004).

Teva raises one additional argument to support its narrow construction. It alleges that because the patentees neither described nor enabled the making of "spheroids" by any method other than by extrusion and spheronization, the term "spheroid" should be limited to maintain the validity of claims 13 and 14. (Teva's Br. at 28). Teva notes that the named inventors were aware of other methods of making "spheroids," but did not disclose them to the public. Absent that disclosure, Teva contends that the claims are not enabled or described. This argument is flawed. A court should not construe a claim term to preserve a claim's validity unless, "after applying all the available tools of claim construction," the claim term remains ambiguous. *Liebel-Flarsheim*, 358 F.3d at 911. Here, the term "spheroid" is not ambiguous and, therefore, the Court will not embark on a validity analysis at this time.

In conclusion, the Court finds that "spheroids" should not be limited to a particular method of manufacture. As such, the Court finds that "spheroids" means "one or more particles that are generally shaped like a sphere, although they do not have to be perfectly round."

3. **"with diminished incidence(s) of nausea and emesis"**

The parties agree that the meaning of the term "incidence" should include "frequency" of an occurrence or event. (Chart). They disagree, however, whether it should include "degree" or "level." (*See id.*).

The claims that contain this limitation are unilluminating. *See, e.g.*, '171 patent, claims 20, 22-23. Therefore, the Court begins by looking at the specification. Both parties refer to the same passage in the specification to support their construction:

> The use of the one-a-day venlafaxine hydrochloride formulations of this invention reduces by adaptation, the level of nausea and incidence of emesis that attend the administration of multiple daily dosing. In clincial trials of venlafaxine hydrochloride ER, the probability of developing nausea in the course of the trials was greatly reduced after the first week. Venlafaxine ER showed a statistically significant improvement over conventional venlafaxine hydrochloride tablets in two eight-week and one 12 week clinical studies. Thus, in accordance with this use aspect of the invention there is provided a method for reducing the level of nausea and incidence of emesis attending the administration of venlafaxine hydrochloride which comprises dosing a patient in need of treatment with venlafaxine hydrochloride with an extended release formulation of venlafaxine hydrochloride once a day in a therapeutically effective amount.

'171 patent, col. 2, lines 45-62 (emphasis added).

Both parties agree that the reference to "level," as used in the above passage, connotes degree. They disagree, however, on what affect, if any, that has on the meaning of "incidence."

Teva contends that the passage above distinguishes between "level," i.e., degree, and "incidence," i.e., frequency. Teva further points out that the claims do not use level or degree; rather, they only refer to "incidence." Wyeth contends that the passage equates "incidence" with "level," thereby broadening the meaning of the term to include degree. Wyeth also juxtaposes the above passage with an excerpt that appears earlier in the specification:

> With the plural daily dosing regimen, the most common side effect is nausea, experienced by about forty five percent of patients under treatment with venlafaxine hydrochloride. Vomiting also occurs in about seventeen percent of the patients.

'171 patent, col. 2, lines 7-11 (emphasis added). Wyeth asserts that this passage demonstrates that when the patentees meant to refer to the number of patients experiencing a side effect, they did so by stating that they were "experienced by" or "occurs in" a certain "percent" of patients. Significantly, according to Wyeth, the patentees did not equate percent with "incidence." Thus, Wyeth asserts "incidence" is broader than frequency.

Wyeth's argument is inapt. Simply because the patentees did not use the word "incidence" in the earlier passage does not by itself redefine "incidence." Rather, that passage makes clear that the patentees were concerned with the number of patients experiencing side effects, not necessarily the severity of those side effects. Moreover, the abstract states that the invention "provides a lower incidence of nausea and vomiting than the conventional tablets." '171 patent, Abstract (emphasis added). Because the only discussion of the conventional tablets in the specification that is relevant to the term "incidence" concerns the percent of patients that experienced side effects, the abstract supports a narrow construction.

Ultimately, Teva appears to be correct that the patentees drew a distinction between "level" and "incidence." Although the specification refers to both terms, the claims only recite "incidence." If indeed "incidence" meant the same thing as "level," or was broader, it begs the question why the word "level" was used in the first place. The reason must be because the patentees meant to differentiate between the two terms. It is clear from the specification that when the patentees wanted to refer to "incidence," they did. Thus, the term "incidence" will be limited to its ordinary meaning as informed by the specification.

Lastly, it is worth noting that "[t]he fact that a patent asserts that an invention achieves several objectives does not require that each of the claims be construed as limited to structures that are capable of achieving all of the objectives." *Liebel-Flarsheim*, 358 F.3d at 908. Thus, the fact that the patents may discuss a reduced "level" and "incidence" of nausea does not require that claims using the word "incidence" encompass both benefits. In addition, the "incidence" limitation is not present in all of the asserted claims. *See, e.g.*, '171 patent, claims 21, 24-25; '958 patent, claims 2, 5-6. Therefore, to the extent that Wyeth suggests that a narrow construction of this term unjustifiably excludes one of the primary benefits of the invention, namely the reduction in degree of side effects, that is not the case for all asserted claims. The asserted claims that do not contain the "incidence" limitation are obviously broader and would read on such benefits.

Furthermore, to the extent that Wyeth relies on extrinsic evidence to support its broad construction, the Court does not find that evidence particularly helpful. The specification draws a clear distinction between "incidence" and "level." General dictionary definitions that allegedly support a broader construction ignore the context within which the patents use the term. *See,*

e.g., Concise Oxford Dict. of Current English 614 (5th ed. 1964) (defining "incidence" as "range, scope, extent, of influence"). The Federal Circuit in *Phillips* warned of relying on such definitions: "[H]eavy reliance on the dictionary divorced from the intrinsic evidence risks transforming the meaning of the claim term to the artisan into the meaning of the term in the abstract, out of its particular context, which is the specification." *Phillips*, 415 F.3d at 1321. In any event, other dictionaries define the term as limited to frequency. *See* Webster's Third New Int'l Dict. (Unabridged) 1142 (2002) (defining "incidence" as "rate, range, or amount of occurrence or influence . . . *sometimes*: the rate of occurrence of new cases of a particular disease in a population being studied") (emphasis in original); Taber's Cyclopedic Med. Dict. 1077 (19th ed. 2001) (defining "incidence" as "the frequency of new cases of a disease or condition in a specific population or group"). These dictionaries provide a common meaning that is more fitting given the distinction the specification draws between "incidence" and "level."

Wyeth's experts' opinions, which remove the term "incidence" from its proper context, are also given no weight. *See Phillips*, 415 at 1318 (stating that a court "should discount any expert testimony 'that is clearly at odds with the claim construction mandated by the claims themselves, the written description, and the prosecution history, in other words, with the written record of the patent'") (quoting *Key Pharms. v. Hercon Labs. Corp.*, 161 F.3d 709, 716 (Fed. Cir. 1998)). Further, these experts' opinions are countered by Teva's experts, who opine that the common meaning of "incidence" is consistent with only frequency. *See* Schoenfeld Expert Report ¶ 9; Morrow Expert Report ¶ 11.

Accordingly, the Court finds that "with diminished incidence(s) of nausea and emesis" means "a decrease in the number of patients suffering from nausea and vomiting compared to

patients receiving the same total daily dose of an immediate release formulation that is administered at least twice a day."

4. **"encapsulated"**

Wyeth asserts that "encapsulated" means "[a] formulation that is present in a capsule, i.e., one that is filled into a pharmaceutically acceptable capsule." (Chart). Teva essentially proposes two different constructions depending on how the Court construes the term "extended release formulation." If the Court construes "extended release formulation" broadly to not include any particular ingredients, Teva contends that "encapsulated" means "[a] formulation that is present in a capsule." (*Id.*). On the other hand, if the Court construes "extended release formulation" to include particular ingredients, Teva agrees with Wyeth's narrower construction. (*See, e.g.*, Teva's Br. at 29 ("If the Court adopts Teva's construction of the term 'extended release formulation,' there is no dispute concerning the term "encapsulated.")).

Although the Court disagrees with Teva's argument that the construction of the term "encapsulated" is contingent on the construction of "extended release formulation," there appears to be no need for this Court to perform an exhaustive analysis of how this term should be construed because the Court has adopted the narrower construction of "extended release formulation." That being the case, the parties do not dispute the meaning of the term "encapsulated." Accordingly, the Court finds that "encapsulated" means "a formulation that is filled into a pharmaceutically acceptable capsule."

CONCLUSION

For the aforementioned reasons, the Court construes the disputed claim terms as follows:

1. "extended release formulation" means "a formulation comprising venlafaxine hydrochloride, microcrystalline cellulose and, optionally, HPMC coated with a mixture of ethyl cellulose and HPMC in an amount needed to provide a specific unit dosage administered once-a-day to provide a therapeutic blood plasma level of venlafaxine over the entire 24-hour period of administration;"

2. "spheroids" means "one or more particles that are generally shaped like a sphere, although they do not have to be perfectly round;"

3. "with diminished incidence(s) of nausea and emesis" means "a decrease in the number of patients suffering from nausea and vomiting compared to patients receiving the same total daily dose of an immediate release formulation that is administered at least twice a day;"

4. "encapsulated" means "a formulation that is filled into a pharmaceutically acceptable capsule."

Dated: September 6, 2005

s/ William J. Martini
William J. Martini, U.S.D.J.

EXHIBIT C

US006274171B1

(12) **United States Patent**
Sherman et al.

(10) **Patent No.: US 6,274,171 B1**
(45) **Date of Patent: Aug. 14, 2001**

(54) **EXTENDED RELEASE FORMULATION OF VENLAFAXINE HYDROCHLORIDE**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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Related U.S. Application Data

(63) Continuation-in-part of application No. 08/964,328, filed on Nov. 5, 1997, now abandoned, which is a continuation-in-part of application No. 08/821,137, filed on Mar. 20, 1997, now abandoned.

(60) Provisional application No. 60/014,006, filed on Mar. 25, 1996.

(51) **Int. Cl.**[7] **A61K 9/52**; A61K 9/54; A61K 9/62

(52) **U.S. Cl.** **424/461**; 424/457; 424/458; 424/459; 514/781; 514/962

(58) **Field of Search** 424/495, 494, 424/461, 458, 459, 457, 456, 462

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(57) **ABSTRACT**

This invention relates to a 24 hour extended release dosage formulation and unit dosage form thereof of venlafaxine hydrochloride, an antidepressant, which provides better control of blood plasma levels than conventional tablet formulations which must be administered two or more times a day and further provides a lower incidence of nausea and vomiting than the conventional tablets. More particularly, the invention comprises an extended release formulation of venlafaxine hydrochloride comprising a therapeutically effective amount of venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and, optionally, hydroxypropylmethylcellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose.

25 Claims, No Drawings

EXTENDED RELEASE FORMULATION OF VENLAFAXINE HYDROCHLORIDE

This application continuation-in-part of Application Ser. No. 08/964,328, filed Nov. 5, 1997 abandoned, which is a continuation-in-part of Application Ser. No. 08/821,137, filed Mar. 20, 1997 abandoned, which, in turn, claims priority from Provisional Application No. 60/014,006 filed Mar. 25, 1996.

BACKGROUND OF THE INVENTION

Extended release drug formulations are conventionally produced as compressed tablets by hydrogel tablet technology. To produce these sustained release tablet drug dosage forms, the active ingredient is conventionally compounded with cellulose ethers such as methyl cellulose, ethyl cellulose or hydroxypropylmethylcellulose with or without other excipients and the resulting mixture is pressed into tablets. When the tablets are orally administered, the cellulose ethers in the tablets swell upon hydration from moisture in the digestive system, thereby limiting exposure of the active ingredient to moisture. As the cellulose ethers are gradually leached away by moisture, water more deeply penetrates the gel matrix and the active ingredient slowly dissolves and diffuses through the gel, making it available for absorption by the body. An example of such a sustained release dosage form of the analgesic/anti-inflammatory drug etodolac (Lodine®) appears in U.S. Pat. No. 4,966,768. U.S. Pat. No. 4,389,393 discloses sustained release therapeutic compressed solid unit dose forms of an active ingredient plus a carrier base comprised of a high molecular weight hydroxypropylmethylcellulose, methyl cellulose, sodium carboxymethylcellulose and or other cellulose ether.

Where the production of tablets is not feasible, it is conventional in the drug industry to prepare encapsulated drug formulations which provide extended or sustained release properties. In this situation, the extended release capsule dosage forms may be formulated by mixing the drug with one or more binding agents to form a uniform mixture which is then moistened with water or a solvent such as ethanol to form an extrudable plastic mass from which small diameter, typically 1 mm, cylinders of drug/matrix are extruded, broken into appropriate lengths and transformed into spheroids using standard spheronization equipment. The spheroids, after drying, may then be film-coated to retard dissolution. The film-coated spheroids may then be placed in pharmaceutically acceptable capsules, such as starch or gelatin capsules, in the quantity needed to obtain the desired therapeutic effect. Spheroids releasing the drug at different rates may be combined in a capsule to obtain desired release rates and blood levels. U.S. Pat. No. 4,138,475 discloses a sustained release pharmaceutical composition consisting of a hard gelatin capsule filled with film-coated spheroids comprised of propanolol in admixture with microcrystalline cellulose wherein the film coating is composed of ethyl cellulose, optionally, with hydroxypropylmethylcellulose and/or a plasticizer.

Venlafaxine, 1-[2-dimethylamino)-1-(4-methoxyphenyl) ethyl]cyclohexanol, is an important drug in the neuropharmacological arsenal used for treatment of depression. Venlafaxine and the acid addition salts thereof are disclosed in U.S. Pat. No. 4,535,186. Venlafaxine hydrochloride is presently administered to adults in compressed tablet form in doses ranging from 75 to 350 mg/day, in divided doses two or three times a day. In therapeutic dosing with venlafaxine hydrochloride tablets, rapid dissolution results in a rapid increase in blood plasma levels of the active compound shortly after administration followed by a decrease in blood plasma levels over several hours as the active compound is eliminated or metabolized, until subtherapeutic plasma levels are approached after about twelve hours following administration, thus requiring additional dosing with the drug. With the plural daily dosing regimen, the most common side effect is nausea, experienced by about forty five percent of patients under treatment with venlafaxine hydrochloride. Vomiting also occurs in about seventeen percent of the patients.

BRIEF DESCRIPTION OF THE INVENTION

In accordance with this invention, there is provided an extended release (ER), encapsulated formulation containing venlafaxine hydrochloride as the active drug s component, which provides in a single dose, a therapeutic blood serum level over a twenty four hour period.

Through administration of the venlafaxine formulation of this invention, there is provided a method for obtaining a flattened drug plasma concentration to time profile, thereby affording a tighter plasma therapeutic range control than can be obtained with multiple daily dosing. In other words, this invention provides a method for eliminating the sharp peaks and troughs (hills and valleys) in blood plasma drug levels induced by multiple daily dosing with conventional immediate release venlafaxine hydrochloride tablets. In essence, the plasma levels of venlafaxine Is hydrochloride rise, after administration of the extended release formulations of this invention, for between about five to about eight hours (optimally about six hours) and then begin to fall through a protracted, substantially linear decrease from the peak plasma level for the remainder of the twenty four hour period, maintaining at least a threshold therapeutic level of the drug during the entire twenty-four period. In contrast, the conventional immediate release venlafaxine hydrochloride tablets give peak blood plasma levels in 2 to 4 hours. Hence, in accordance with the use aspect of this invention, there is provided a method for moderating the plural blood plasma peaks and valleys attending the pharmacokinetic utilization of multiple daily tablet dosing with venlafaxine hydrochloride which comprises administering to a patient in need of treatment with venlafaxine hydrochloride, a one-a-day, extended release formulation of venlafaxine hydrochloride.

The use of the one-a-day venlafaxine hydrochloride formulations of this invention reduces by adaptation, the level of nausea and incidence of emesis that attend the administration of multiple daily dosing. In clinical trials of venlafaxine hydrochloride ER, the probability of developing nausea in the course of the trials was greatly reduced after the first week. Venlafaxine ER showed a statistically significant improvement over conventional venlafaxine hydrochloride tablets in two eight-week and one 12 week clinical studies. Thus, in accordance with this use aspect of the invention there is provided a method for reducing the level of nausea and incidence of emesis attending the administration of venlafaxine hydrochloride which comprises dosing a patient in need of treatment with venlafaxine hydrochloride with an extended release formulation of venlafaxine hydrochloride once a day in a therapeutically effective amount.

The formulations of this invention comprise an extended release formulation of venlafaxine hydrochloride comprising a therapeutically effective amount of venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and, optionally,

hydroxypropylmethylcellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose. Unless otherwise noted, the percentage compositions mentioned herein refer to percentages of the total weight of the final composition or formulation.

More particularly, the extended release formulations of this invention are those above wherein the spheroids are comprised of from about 6% to about 40% venlafaxine hydrochloride by weight, about 50% to about 95% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

A preferred embodiment of this invention are formulations wherein the spheroids are comprised of about 30% to about 40% venlafaxine hydrochloride by weight, about 50% to about 70% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

Another preferred lower dose formulation of this invention are those wherein the spheroids are comprised less than 30% venlafaxine hydrochloride. These formulations comprise spheroids of from about 6% to about 30% venlafaxine hydrochloride by weight, about 70% to about 94% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

Within this subgroup of lower dose formulations are formulations in which the spheroids are comprised of from about 6% to about 25% venlafaxine hydrochloride and from about 94% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose. Another preferred subgroup of spheroids in these formulations comprises from about 6% to about 25% venlafaxine hydrochloride and from about 94% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose. A further preferred subgroup of spheroids in these formulations comprises from about 6% to about 20% venlafaxine hydrochloride and from about 94% to about 80% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose. Within each of these subgroups is understood to be formulations in which the spheroids are comprised of venlafaxine HCl and microcrystalline cellulose in the amounts indicated, with no hydroxypropylmethylcellulose present. Each of these formulations is also preferably contained in a gelatin capsule, preferably a hard gelatin capsule.

DETAILED DESCRIPTION OF THE INVENTION

1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride is polymorphic. Of the forms isolated and characterized to date, Form I is considered to be the kinetic product of crystallization which can be converted to Form II upon heating in the crystallization solvent. Forms I and II cannot be distinguished by their melting points but do exhibit some differences in their infrared spectra and X-ray diffraction patterns. Any of the polymorphic forms such as Form I or Form II may be used in the formulations of the present invention.

The extended release formulations of this invention are comprised of 1-[2-(dimethylamino)-1-(4-methoxyphenyl) ethyl]cyclohexanol hydrochloride in admixture with microcrystalline cellulose and hydroxypropylmethylcellulose. Formed as beads or spheroids, the drug containing formulation is coated with a mixture of ethyl cellulose and hydroxypropylmethyl cellulose to provide the desired level of coating, generally from about two to about twelve percent on a weight/weight basis of final product or more preferably from about five to about ten percent (w/w), with best results obtained at from about 6 to about 8 percent (w/w). More specifically, the extended release spheroid formulations of this invention comprise from about 30 to 40 percent venlafaxine hydrochloride, from about 50 to about 70 percent microcrystalline cellulose, NF, from about 0.25 to about I percent hydroxypropylmethylcellulose, USP, and from about 5 to about 10 percent film coating, all on a weight/weight basis. And preferably, the spheroid formulations contain about 35 percent venlafaxine hydrochloride, about 55 to 60 percent microcrystalline cellulose NF (Avicel® PH101), about one half percent hydroxypropylmethylcellulose 2208 USP (K3, Dow, which has a viscosity of 3 cps for 2% aqueous solutions, a methoxy content of 19–24% and a hydroxypropoxy content of 4–13%), and from about 6 to 8 percent film coating.

The film coating is comprised of 80 to 90 percent of ethyl cellulose, NF and 10 to 20 percent hydroxypropylmethylcellulose (2910), USP on a weight/weight basis. Preferably the ethyl cellulose has a ethoxy content of 44.0–51% and a viscosity of 50 cps for a 5% aqueous solution and the hydroxypropylmethylcellulose is USP 2910 having a viscosity of 6 cps at 2% aqueous solution with a methoxy content of 28–30% and a hydroxypropoxy content of 7–12%. The ethyl cellulose used herein is Aqualon HG 2834.

Other equivalents of the hydroxypropylmethylcelluloses 2208 and 2910 USP and ethyl cellulose, NF, having the same chemical and physical characteristics as the proprietary products named above may be substituted in the formulation without changing the inventive concept. Important characteristics of suitable hydroxypropylmethylcelluloses include a low viscosity, preferably less than 10 cps and more preferably 2–5 cps, and a gel temperature above that of the temperature of the extrudate during extrusion. As explained below, these and other characteristics which enable the extrudate to remain moist and soft (pliable) are preferred for the hydroxypropylmethylcellulose. In the examples below, the extrudate temperature was generally 50–55° C.

It was completely unexpected that an extended release formulation containing venlafaxine hydrochloride could be obtained because the hydrochloride of venlafaxine proved to be extremely water soluble. Numerous attempts to produce extended release tablets by hydrogel technology proved to be fruitless because the compressed tablets were either physically unstable (poor compressibility or capping problems) or dissolved too rapidly in dissolution studies. Typically, the tablets prepared as hydrogel sustained release formulations gave 40–50% dissolution at 2 hrs, 60–70% dissolution at 4 hrs and 85–100% dissolution at 8 hrs.

Numerous spheroid formulations were prepared using different grades of microcrystalline cellulose and hydroxypropylmethylcellulose, different ratios of venlafaxine hydrochloride and filler, different binders such as polyvinylpyrrolidone, methylcellulose, water, and polyethylene glycol of different molecular weight ranges in order to find a formulation which would provide a suitable granulation mix which could be extruded properly. In the extrusion process, heat buildup occurred which dried out the extrudate so much that it was difficult to convert the extruded cylinders into spheroids. Addition of hydroxypropylmethylcellulose 2208 to the venlafaxine hydrochloride-microcrystalline cellulose mix made production of spheroids practical.

The encapsulated formulations of this invention may be produced in a uniform dosage for a specified dissolution profile upon oral administration by techniques understood in the art. For instance, the spheroid components may be blended for uniformity with a desired concentration of active ingredient, then spheronized and dried. The resulting spheroids can then be sifted through a mesh of appropriate pore size to obtain a spheroid batch of uniform and prescribed size.

The resulting spheroids can be coated and resifted to remove any agglomerates produced in the coating steps. During the coating process samples of the coated spheroids may be tested for their distribution profile. If the dissolution occurs too rapidly, additional coating may be applied until the spheroids present a desired dissolution rate.

The following examples are presented to illustrate applicant's solution to the problem of preparation of the extended release drug containing formulations of this invention.

EXAMPLE NO. 1

Venlafaxine Hydrochloride Extended Release Capsules

A mixture of 44.8 parts (88.4% free base) of venlafaxine hydrochloride, 74.6 parts of the microcrystalline cellulose, NF, and 0.60 parts of hydroxypropylmethyl cellulose 2208, USP, are blended with the addition of 41.0 parts water. The plastic mass of material is extruded, spheronized and dried to provide uncoated drug containing spheroids.

Stir 38.25 parts of ethyl cellulose, NF, HG2834 and 6.75 parts of hydroxypropylmethylcellulose 2910, USP in a 1:1 v/v mixture of methylene chloride and anhydrous methanol until solution of the film coating material is complete.

To a fluidized bed of the uncoated spheroids is applied 0.667 parts of coating solution per part of uncoated spheroids to obtain extended release, film coated spheroids having a coating level of 3%.

The spheroids are sieved to retain the coated spheroids of a particle size between 0.85 mm to 1.76 mm diameter. These selected film coated spheroids are filled into pharmaceutically acceptable capsules conventionally, such as starch or gelatin capsules.

EXAMPLE NO. 2

Same as for Example 1 except that 1.11 parts of the film coating solution per part of uncoated spheroids is applied to obtain a coating level of 5%.

EXAMPLE NO. 3

Same as for Example 1 except that 1.33 parts of the film coating solution is applied to 1 part of uncoated spheroids to obtain a coating level of 6%.

EXAMPLE NO. 4

Same as for Example 1 except that 1.55 parts of the film coating solution is applied to 1 part of uncoated spheroids to obtain a coating level of 7%.

In the foregoing failed experiments and in Examples 1–4, the extrusion was carried out on an Alexanderwerk extruder. Subsequent experiments carried out on Hutt and Nica extruders surprisingly demonstrated that acceptable, and even improved, spheroids could be made without the use of an hydroxypropylmethylcellulose.

In such further experiments the applicability of the invention was extended to formulations wherein the weight percentage of venlafaxine hydrochloride is 6% to 40%, preferably 8% to 35%. Thus, the extended release spheroid formulations of this invention comprise from about 6 to about 40 percent venlafaxine hydrochloride, from about 50 to about 94 percent microcrystalline cellulose, NF, optionally, from about 0.25 to about 1 percent hydroxypropylmethylcellulose, and from about 2 to about 12 percent, preferably about 3 to 9 percent, film coating.

Spheroids of the invention were produced having 8.25% (w/w) venlafaxine hydrochloride and the remainder (91.75%, w/w) being microcrystalline cellulose, with a coating of from 3 to 5% (w/w), preferably 4%, of the total weight. The spheroids with 8.25% venlafaxine hydrochloride and 4% coating were filled into No. 2 white opaque shells with a target fill weight of 236 mg.

Further spheroids of the invention were produced having 16.5% (w/w) venlafaxine hydrochloride and the remainder (83.5%,w/w) being microcrystalline cellulose, with a coating of from 4 to 6% (w/w), preferably 5%, of the total weight. The spheroids 16.5% venlafaxine hydrochloride and 5% coating were filled into No. 2 white opaque shells with a target fill weight of 122 mg.

The test for acceptability of the coating level is determined by analysis of the dissolution rate of the finished coated spheroids prior the encapsulation. The dissolution procedure followed uses USP Apparatus 1 (basket) at 100 rpm in purified water at 37° C.

Conformance with the dissolution rate given in Table 1 provides the twenty-four hour therapeutic blood levels for the drug component of the extended release capsules of this invention in capsule form. Where a given batch of coated spheroids releases drug too slowly to comply with the desired dissolution rate study, a portion of uncoated spheroids or spheroids with a lower coating level may be added to the batch to provide, after thorough mixing, a loading dose for rapid increase of blood drug levels. A batch of coated spheroids that releases the drug too rapidly can receive additional film-coating to give the desired dissolution profile.

TABLE 1

Acceptable Coated Spheroid Dissolution Rates

Time (hours)	Average % Venlafaxine HCl released
2	<30
4	30–55
8	55–80
12	65–90
24	>80

Batches of the coated venlafaxine hydrochloride containing spheroids which have a dissolution rate corresponding to that of Table 1 are filled into pharmaceutically acceptable

capsules in an amount needed to provide the unit dosage level desired. The standard unit dosage immediate release (IR) tablet used presently provides amounts of venlafaxine hydrochloride equivalent to 25 mg, 37.5 mg, 50 mg, 75 mg and 100 mg venlafaxine. The capsules of this invention are filled to provide an amount of venlafaxine hydrochloride equivalent to that presently used in tablet form and also up to about 150 mg venlafaxine hydrochloride.

Dissolution of the venlafaxine hydrochloride ER capsules is determined as directed in the U. S. Pharmacopoeia (USP) using apparatus 1 at 100 rpm on 0.9 L of water. A filtered sample of the dissolution medium is taken at the times specified. The absorbance of the clear solution is determined from 240 to 450 nanometers (nm) against the dissolution medium. A baseline is drawn from 450 nm through 400 nm and extended to 240 nm. The absorbance at the wavelength of maximum absorbance (about 274 nm) is determined with respect to this baseline. Six hard gelatin capsules are filled with the theoretical amount of venlafaxine hydrochloride spheroids and measured for dissolution. Standard samples consist of venlafaxine hydrochloride standard solutions plus a gelatin capsule correction solution.

The percentage of venlafaxine released is determined from the equation

$$\%\ \text{Venlafaxine hydrochloride released} = \frac{(As)(Wr)(S)(Vl)(0.888)(100)}{(Ar)(V2)(C)}$$

where As is absorbance of sample preparation, Wr is weight of reference standard, mg; S is strength of the reference standard, decimal; V1 is the volume of dissolution medium used to dissolve the dosage form, mL; 0.884 is the percent free base, Ar is the absorbance of the standard preparation, V2 is the volume of reference standard solution, mL; and C is the capsule claim in mg.

Table 2 shows the plasma level of venlafaxine versus time for one 75 mg conventional Immediate Release (IR) tablet administered every 12 hours, two 75 mg extended release (ER) capsules administered simultaneously every 24 hours, and one 150 mg extended release (ER) capsule administered once every 24 hours in human male subjects. The subjects were already receiving venlafaxine hydrochloride according to the dosage protocol, thus the plasma blood level at zero time when dosages were administered is not zero.

TABLE 2

Plasma venlafaxine level (ng/mL) versus time, conventional tablet (not extended release) versus ER capsule

Time (hours)	75 mg (IR)tablet (q 12 h)	2 × 75 mg (ER)capsules (q 24 hr)	1 × 150 mg (ER)capsules (q 24 h)
0	62.3	55.0	55.8
0.5	76.3		
1	135.6	53.3	53.2
2	212.1	69.8	70.9
4	162.0	138.6	133.3
6	114.6	149.0	143.5
8	86.7	129.3	129.5
10		118.4	114.4
12	51.9	105.1	105.8
12.5	74.7		
13	127.5		
14	161.3	90.5	91.3
16	134.6	78.2	78.5
18	106.2		

TABLE 2-continued

Plasma venlafaxine level (ng/mL) versus time, conventional tablet (not extended release) versus ER capsule

Time (hours)	75 mg (IR)tablet (q 12 h)	2 × 75 mg (ER)capsules (q 24 hr)	1 × 150 mg (ER)capsules (q 24 h)
20	83.6	62.7	63.3
24	57.6	56.0	57.3

Table 2 shows that the plasma levels of two 75 mg/capsule venlafaxine hydrochloride ER capsules and one 150 mg/capsule venlafaxine hydrochloride ER capsule provide very similar blood levels. The data also show that the plasma level after 24 hours for either extended release regimen is very similar to that provided by two immediate release 75 mg tablets of venlafaxine hydrochloride administered at 12 hours intervals.

Further, the plasma levels of venlafaxine obtained with the extended release formulation do not increase to the peak levels obtained with the conventional immediate release tablets given 12 hours apart. The peak level of venlafaxine from (ER), somewhat below 150 ng/ml, is reached in about six hours, plus or minus two hours, based upon this specific dose when administered to patients presently under treatment with venlafaxine hydrochloride (IR). The peak plasma level of venlafaxine, somewhat over 200 ng/ml, following administration of (IR) is reached in two hours and falls rapidly thereafter.

Table 3 shows venlafaxine blood plasma levels in male human subjects having a zero initial blood plasma level. Again, a peak blood plasma concentration of venlafaxine is seen at about 6 hours after dosing with venlafaxine hydrochloride extended release capsules in the quantities indicated. The subjects receiving the single 50 mg immediate release tablet showed a peak plasma level occurring at about 4. hours. For comparative purposes, the plasma levels of venlafaxine for subjects receiving the conventional formulated tablet can be multiplied by a factor of three to approximate the plasma levels expected for a single dose of 150 mg. conventional formulation.

TABLE 3

Plasma Blood Levels in Human Males Having No Prior Venlafaxine Blood Level

Time (Hours)	1 × 50 mg IR tablet	2 × 75 mg ER capsules	1 × 150 mg ER capsule
0	0	0	0
1	27.87	1.3	0
1.5	44.12	6.0	2.2
2	54.83	20.6	12.8
4	66.38	77.0	81.0
6	49.36	96.5	94.4
8	30.06	93.3	86.9
10	21.84	73.2	72.8
12	15.91	61.3	61.4
14	13.73	52.9	51.9
16	10.67	47.5	41.1
20	5.52	35.2	34.0
24	3.56	29.3	28.5
28	2.53	23.4	22.9
36	1.44	11.9	13.5
48	0.66	5.8	5.2

The blood plasma levels of venlafaxine were measured according to the following procedure. Blood samples from the subjects were collected in heparinized evacuated blood tubes and the tubes were inverted gently several times. As

quickly as possible, the tubes were centrifuged at 2500 rpm for 15 minutes. The plasma was pipetted into plastic tubes and stored at −20° C. until analysis could be completed.

To 1 mL of each plasma sample in a plastic tube was added 150 μL of a stock internal standard solution (150 μg/ml). Saturated sodium borate (0.2 mL) solution was added to each tube and vortexed. Five mL of ethyl ether was added to each tube which were then capped and shaken for 10 minutes at high speed. The tubes were centrifuged at 3000 rpm for 5 minutes. The aqueous layer was frozen in dry ice and the organic layer transferred to a clean screw cap tube. A 0.3 mL portion of 0.01 N HCl solution was added to each tube and shaken for 10 minutes at high speed. The aqueous layer was frozen and the organic layer removed and discarded. A 50 μL portion of the mobile phase (23:77 acetonitrile:0.1M monobasic ammonium phosphate buffer, pH 4.4) was added to each tube, vortexed, and 50 μL samples were injected on a Supelco Supelcoil LC-8-DB, 5 cm×4.6 mm, 5 μ; column in a high pressure liquid chromatography apparatus equipped with a Waters Lambda Max 481 detector or equivalent at 229 nm. Solutions of venlafaxine hydrochloride at various concentrations were used as standards.

EXAMPLE NO. 5

Manufactured by the techniques described herein, another preferred formulation of this invention comprises spheroids of from about 30% to about 35% venlafaxine hydrochloride and from about 0.3% to about 0.6% hydroxypropylmethylcellulose. These spheroids are then coated with a film coating, as described above, to a coating level of from about 5% to about 9%, preferably from about 6% to about 8%. A specific formulation of this type comprises spheroids of about 33% venlafaxine hydrochloride and about 0.5% hydroxypropylmethylcellulose, with a film coating of about 7%.

Lower dosage compositions or formulations of this invention may also be produced by the techniques described herein. These lower dosage forms may be administered alone for initial titration or initiation of treatment, prior to a dosage increase. They may also be used for an overall low-dose administration regimen or in combination with higher dosage compositions, such as capsule formulations, to optimize individual dosage regimens.

These lower dose compositions may be used to create encapsulated formulations, such as those containing doses of venlafaxine hydrochloride from about 5 mg to about 50 mg per capsule. Particular final encapsulated dosage forms may include, but are not limited to, individual doses of 7.5 mg, 12.5 mg, 18.75 mg, or 28.125 mg of venlafaxine HCl per capsule.

The spheroids useful in these lower dose formulations may comprise from about 5% to about 29.99% venlafaxine HCl, preferably from about 5% to about 25%, from about 75% to about 95% microcrystalline cellulose, and, optionally from about 0.25% to about 1.0% hydroxypropylmethylcellulose. The spheroids may be coated as described above, preferably with a film coating of from about 5% to about 10% by is weight. In some preferred formulations, the spheroids comprise the cited venlafaxine HCl and microcrystalline cellulose, with no hydroxypropylmethyl cellulose.

EXAMPLE NO. 6

Spheroids comprising 16.5% venlafaxine HCl and 83.5% microcrystalline cellulose were mixed with approximately 50% water (w/w) to granulate in a Littleford Blender Model FM-50E/1Z (Littleford Day Inc., P.O. Box 128, Florence, Ky. 41022-0218, U.S.A.) at a fixed speed of 180 rpm. The blended material was extruded through a 1.25 mm screen using a Nica extruder/speronization machine (Aeromatic-Fielder Division, Niro Inc., 9165 Rumsey Rd., Columbia, Md. 21045, U.S.A.) for a 12/20 mesh cut after drying. Two portions of the resulting spheroids were coated with a 5% and 7% coating level, respectively, by techniques described above using the coating formulation:

Ingredient	% (w/w)
Methylene Chloride	60.000
Methanol Anhydrous	35.500
Ethylcellulose, NF, HG 2834, 50 cps	3.825
Hydroxypropyl Methylcellulose, 2910 USP, 6 cps	0.675

These 5% and 7% coated lots were tested for dissolution on a Hewlett Packard automated dissolution system over a 24 hour period, resulting in the following dissolution patterns

Time/hr	% Dissoluded 16.5%/5%	% Dissolved 16.5%/7%
2	12.4	5.6
4	42.8	25.4
8	70.7	60.4
12	82.2	75.4
24	94.3	92.7

EXAMPLE NO. 7

A formulation of spheroids containing 8.25% venlafaxine HCl and 91.75% microcellulose was prepared according to the techniques of Example No. 6 and coated with a 5% film coating. In the Hewlett Packard automated dissolution system these spheroids provided the following dissolution profile:

Time/hr	% Dissolved 8.25%/5%
2	4.4
4	24.2
8	62.9
12	77.8
24	93.5

Thus, the desired dissolution rates of sustained release dosage forms of venlafaxine hydrochloride, impossible to achieve with hydrogel tablet technology, has been achieved with the film-coated spheroid compositions of this invention.

What is claimed is:

1. An extended release formulation of venlafaxine hydrochloride comprising a pharmaceutically acceptable capsule containing spheroids comprised of from about 6% to about 40% venlafaxine hydrochloride by weight, about 50% to about 94% microcrystalline cellulose, NF, by weight, and optionally from about 0.25% to about 1% by weight of hydroxypropyl-methylcellulose, USP, wherein the spheroids are coated with a film coating composition comprised of ethyl cellulose and hydroxypropylmethylcellulose.

2. An extended release formulation of venlafaxine hydrochloride according to claim 1 which provides peak serum levels of up to 150 ng/ml and extended therapeutically effective plasma levels over a twenty four hour period.

3. An extended release formulation according to claim 1 wherein the spheroids are coated with from about 2% to about 12% of total formulation weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

4. An extended release formulation according to claim 1 wherein the spheroids are comprised of from about 30% to 40% venlafaxine hydrochloride by weight, about 50% to about 70% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP.

5. An extended release formulation according to claim 4 wherein the spheroids are coated with from about 2% to about 12% of total formulation weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

6. An extended release formulation according to claim 1 wherein the spheroids comprise from about 6% to about 30% venlafaxine hydrochloride by weight, about 70.1% to about 94% microcrystalline cellulose, NF, by weight and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

7. An extended release formulation according to claim 6 wherein the spheroids are coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

8. An extended release formulation according to claim 1 wherein the spheroids comprise from about 5% to about 25% venlafaxine hydrochloride and from about 95% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

9. An extended release formulation according to claim 6 wherein the spheroids comprise from about 6% to about 25% venlafaxine hydrochloride and from about 94% to about 75% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

10. An extended release formulation according to claim 6 wherein the spheroids comprise from about 6% to about 20% venlafaxine hydrochloride and from about 94% to about 80% microcrystalline cellulose, with an optional amount of from 0.25% to about 1% by weight of hydroxypropylmethylcellulose.

11. An encapsulated, extended release formulation of venlafaxine hydrochloride according to claim 1 having the following dissolution profile in USP Apparatus 1 (basket) at 100 rpm in purified water at 37° C:

Time (hours)	Average % Venlafaxine HCl released
2	<30
4	30–55
8	55–80

-continued

Time (hours)	Average % Venlafaxine HCl released
12	65–90
24	>80

12. An extended release formulation according to claim 1 wherein the spheroids are composed of about 37% by weight of venlafaxine hydrochloride, about 0.5% by weight of hydroxypropylmethylcellulose, and about 62% by weight of microcrystalline cellulose.

13. An extended release formulation according to claim 1 wherein the film coating is comprised of ethyl cellulose (4.81% of total weight) and hydroxypropylmethylcellulose (0.85% of total weight).

14. An extended release formulation according to claim 1 wherein the film coating comprises 6–8% by weight of total weight.

15. An extended release formulation according to claim 1 wherein the film coating is comprised of ethyl cellulose (2.48% of total weight) and hydroxypropylmethylcellulose (0.437% of total weight).

16. An extended release formulation according to claim 1 wherein the film coating composition is comprised of ethyl cellulose having a 44.0–51.0% content of ethoxy groups and hydroxypropylmethylcellulose having a methoxy content of 28.0–30.0% and a hydroxypropoxy group content of 7.0–12.0%.

17. An extended release formulation according to claim 1 wherein the film coating composition is comprised of about 85% by total weight of film coating of ethyl cellulose having 44.0–51% content of ethoxy groups and about 15% by total weight of film coating of hydroxypropylmethylcellulose having a methoxy content of 28.0–30.0% and a hydroxypropoxy group content of 7.0–12.0%.

18. An extended release formulation according to claim 1 wherein the film coating composition is comprised of 85% by weight of ethyl cellulose having an ethoxy content of 44.0–51% and a viscosity of 50% cps for a 5% aqueous solution, and 15% by weight of hydroxypropylmethylcellulose having a viscosity of 6 cps at 2% aqueous solution with a methoxy content of 28–30% and a hydroxypropoxy content of 7–12%.

19. An extended release formulation of venlafaxine hydrochloride for once daily administration which comprises spheroids containing 37.3% venlafaxine, 62.17% microcrystalline cellulose and 0.5% hydroxypropylmethylcellulose coated with a quantity of a mixture comprised of 85% ethyl cellulose and 15% hydroxypropylmethylcellulose sufficient to give coated spheroids having a dissolution profile in USP Apparatus 1 (basket) at 100 rpm in purified water at 37° C.:

Time	Average % Venlafaxine HCl Released
2	<30
4	30–55
8	55–80
12	65–90
24	>80.

20. A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty four hour period with diminished incidences of nausea and emesis which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides

a peak blood plasma level of venlafaxine in from about four to about eight hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

21. A method for eliminating the troughs and peaks of drug concentration in a patients blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about four to about eight hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

22. A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty-four hour period with diminished incidence of nausea and emesis which comprises administering orally to a patient in need thereof, an encapsulated extended release formulation that provides a peak blood plasma level of venlafaxine in from about 5 to about 8 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

23. A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty-four hour period with diminished incidence of nausea and emesis which comprises administering orally to a patient in need thereof, an encapsulated extended release formulation that provides a peak blood plasma level of venlafaxine in about 6 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

24. A method for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about 5 to about 8 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

25. A method for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in about 6 hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

* * * * *

EXHIBIT D

United States Patent [19]

Husbands et al.

[11] **Patent Number: 4,535,186**

[45] **Date of Patent: Aug. 13, 1985**

[54] **2-PHENYL-2-(1-HYDROXYCYCLOALKYL OR 1-HYDROXYCYCLOALK-2-ENYL)ETHYLAMINE DERIVATIVES**

[75] Inventors: **G. E. Morris Husbands, Berwyn; John P. Yardley, Gulph Mills; Eric A. Muth, West Chester, all of Pa.**

[73] Assignee: **American Home Products Corporation, New York, N.Y.**

[21] Appl. No.: **545,701**

[22] Filed: **Oct. 26, 1983**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 486,594, Apr. 19, 1983, abandoned, which is a continuation-in-part of Ser. No. 449,032, Dec. 13, 1982, abandoned.

[51] **Int. Cl.**[3] **C07C 87/28**

[52] **U.S. Cl.** ..... **564/336**; 560/140; 560/250; 560/251; 560/252; 564/157; 564/219; 564/220; 549/443; 549/444; 549/440; 260/465 E

[58] **Field of Search** ..... 564/336, 157, 219, 220; 260/465 E; 560/250, 251, 252, 140; 549/443, 444

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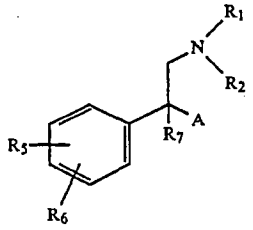
Primary Examiner—Nicky Chan

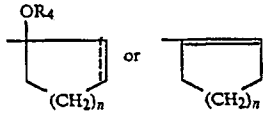
Attorney, Agent, or Firm—Richard K. Jackson

[57] **ABSTRACT**

This invention provides a group of hydroxycycloalkanephenethyl amine antidepressant derivatives of the following structural formula:



in which A is a moiety of the formula



where

the dotted line represents optional unsaturation;

R_1 is hydrogen or alkyl;

R_2 is alkyl;

R_4 is hydrogen, alkyl, formyl or alkanoyl;

R_5 and R_6 are, independently, hydrogen, hydroxyl, alkyl, alkoxy, alkanoyloxy, cyano, nitro, alkylmercapto, amino, alkylamino, dialkylamino, alkanamido, halo, trifluoromethyl or, taken together, methylenedioxy;

R_7 is hydrogen or alkyl; and

n is 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable salt thereof.

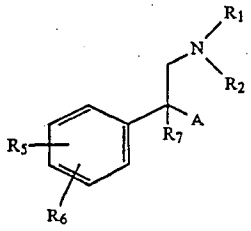
32 Claims, No Drawings

2-PHENYL-2-(1-HYDROXYCYCLOALKYL OR 1-HYDROXYCYCLOALK-2-ENYL)ETHYLAMINE DERIVATIVES

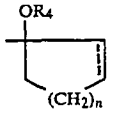
This application is a continuation-in-part of U.S. patent application Ser. No. 486,594, filed Apr. 19, 1983, now abandoned, which application is a continuation-in-part of U.S. patent application Ser. No. 449,032, filed Dec. 13, 1982, now abandoned.

DESCRIPTION OF THE INVENTION

In accordance with this invention there is provided a group of substituted phenethylamine derivatives which are central nervous system antidepressants. The compounds of this invention present the following structural formula:

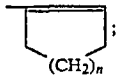


in which A is a moiety of the formula



where

the dotted line represents optional unsaturation, or the analogous cycloalkenyl moiety



R_1 is hydrogen or alkyl of 1 to 6 carbon atoms;

R_2 is alkyl of 1 to 6 carbon atoms;

R_4 is hydrogen, alkyl of 1 to 6 carbon atoms, formyl, or alkanoyl of 2 to 7 carbon atoms;

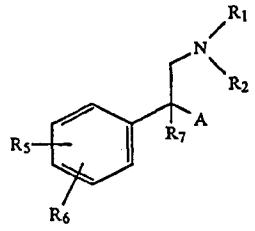
R_5 and R_6 are independently hydrogen, hydroxyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, cyano, nitro, alkylmercapto of 1 to 6 carbon atoms, amino, alkylamino of 1 to 6 carbon atoms, dialkylamino in which each alkyl group is of 1 to 6 carbon atoms, alkanamido of 2 to 7 carbon atoms, halo, trifluoromethyl, or, when taken together, methylene dioxy;

R_7 is hydrogen or alkyl of 1 to 6 carbon atoms; and

n is one of the integers 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable salt thereof.

The preferred compounds are those of the formula:



in which

A is defined supra;

R_1 is hydrogen or alkyl of 1 to 3 carbon atoms;

R_2 is alkyl of 1 to 3 carbon atoms;

R_5 is hydrogen, hydroxy, alkoxy of 1 to 3 carbon atoms, chloro, bromo, trifluoromethyl or alkyl of 1 to 3 carbon atoms;

R_6 is alkyl of 1 to 3 carbon atoms, alkoxy of 1 to 3 carbon atoms, chloro, bromo, trifluoromethyl or alkanoyloxy of 2 to 3 carbon atoms.

R_7 is hydrogen or alkyl of 1 to 3 carbon atoms;

or a pharmaceutically acceptable salt thereof.

The most preferred compounds are those in which R_5 and R_6 are in meta or para positions and n is 2.

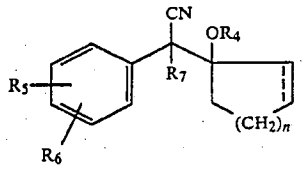
The compounds in which R_4 is formyl or alkanoyl of 2 to 7 carbon atoms are not nearly as potent as the corresponding free hydroxy bearing derivatives in the test procedures employed and disclosed herein. However, in long term therapy the acyloxy derivatives will act as pro drugs as the acyl group is removed in vivo either via acid hydrolysis in the stomach or enzymatically.

The pharmaceutically acceptable acid addition salts of the basic compounds of this invention are formed conventionally by reaction of the free base with an equivalent amount of any acid which forms a non-toxic salt. Illustrative acids are either inorganic or organic, including hydrochloric, hydrobromic, fumaric, maleic, succinic, sulfuric, phosphoric, tartaric, acetic, citric, oxalic and similar acids. For parenteral administration, the use of water soluble salts is preferred, although either the free base of the pharmaceutically acceptable salts are applicable for oral or parenteral administration of the antidepressant agents of this invention. The halo substituent representing R_5 or R_6 is intended to include the chloro, bromo, iodo or fluoro substituents.

The compounds of this invention are produced by reaction of a cycloalkanone or a cycloalkenone with an appropriately substituted (ortho or para) phenylacetonitrile anion following the procedure of Sauvetre et al., Tetrahedron, 34, 2135 (1978) followed by reduction (catalytic hydrogenation, borane reducing agents, $LiAlH_4$, etc.) of the nitrile to a primary amine and alkylation of the amine. In the presence of cyclo aliphatic unsaturation, lithium aluminum hydride is the preferred reducing agent. Subsequent acylation of the α-cycloaliphatic hydroxyl group and any phenolic hydroxyl group present may be effected conventionally with a formylating agent such as formyl fluoride or an alkanoic acid halide or anhydride. Symmetrical N-methylation may be accomplished via a modified Eschweiler-Clarks procedure employing a large excess of water as illustrated by Tilford et al., J.A.C.S. 76, 2431 (1954); alternatively the procedure of Borch and Hassid, J. Org. Chem., 37, 1653 (1972) using sodium cyanoborohydride and formaldehyde may be employed. Non-symmetrical

N-alkylation or monoalkylation may be accomplished by stepwise alkylation of the N-trifluoroacetate as illustrated by R. A. W. Johnstone et al., J. Chem. Soc., (C) 2223 (1969). Where R_4 is alkyl it is introduced prior to reduction of the nitrile by conventional O-alkylation.

The intermediate nitriles prepared during the production of the antidepressant agents of this invention represent an additional aspect of the invention. They are depicted by the structural formula:



in which

the dotted line represents optional unsaturation, and

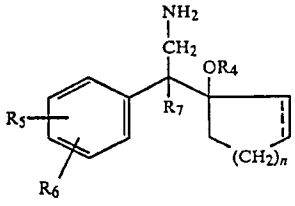
R_4 is hydrogen or alkyl of 1 to 6 carbon atoms;

R_5 and R_6 are ortho or para substituents, independently selected from the group consisting of hydrogen, hydroxyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, aralkoxy of 7 to 9 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, alkylmercapto of 1 to 6 carbon atoms, halo or trifluoromethyl;

R_7 is hydrogen or alkyl of 1 to 6 carbon atoms; and

n is one of the integers 0, 1, 2, 3 or 4.

The intermediate primary amines produced by reduction of the nitrile depicted in the preceding paragraph represent an additional aspect of the invention. They present the following structural formula:



in which

the dotted line represents optional unsaturation,

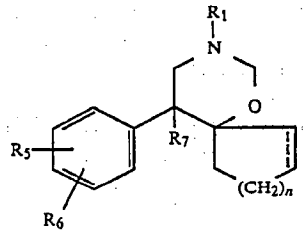
R_4 is hydrogen, or alkyl of 1 to 6 carbon atoms;

R_5 and R_6 are ortho or para substituents independently selected from the group consisting of hydrogen, hydroxyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, aralkoxy of 7 to 9 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, alkylmercapto of 1 to 6 carbon atoms, halo or trifluoromethyl;

R_7 is hydrogen or alkyl of 1 to 6 carbon atoms; and

n is one of the integers 0, 1, 2, 3 or 4.

Symmetrical N,N-dimethylation may be performed readily by reaction of the primary amino derivative with formaldehyde, formic acid in a large excess of water. An intermediate, 3-aza-1-oxaspiro[5.5]undecane, which represents an additional intermediate of this invention is formed during the reaction and is isolatable. It presents the following structural formula:



in which the dotted line represents optional unsaturation,

R_1 is methyl;

R_5 and R_6 are orthor or para substituents independently selected from the group consisting of hydrogen, hydroxyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, aralkoxy of 7 to 9 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, alkylmercapto of 1 to 6 carbon atoms, halo or trifluoromethyl;

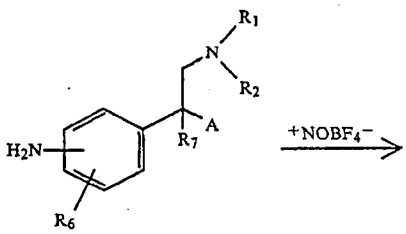
R_7 is hydrogen or alkyl of 1 to 6 carbon atoms; and

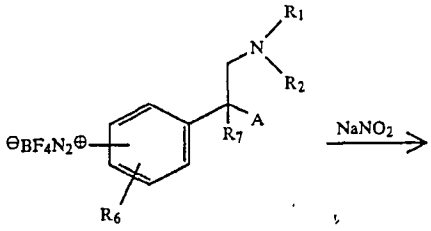
n is one of the integers 0, 1, 2, 3 or 4.

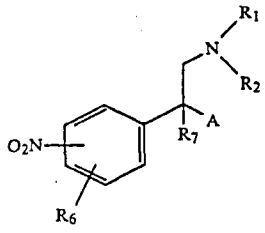
These oxaspiro[5.5]undecane intermediates possess similar activity to the corresponding open-ring tertiary amino end compounds of the invention. For example, the oxazine produced in Example 3 is hereinafter compared, in its properties, with the corresponding dimethylamino end compound of Example 3. The end compound is produced from the corresponding oxazine by prolonged reflux in the presence of aqueous formic acid.

An alternative, and preferred, mode of preparing the compounds of this invention involves the reaction of a cycloalkanone or cycloalkenone with an appropriately substituted phenylacetamide anion following the procedure of Sauvetre et al., ibid., followed by reduction of the amide with lithium aluminum hydride or a borane reducing agent, except in the case of cycloaliphatic unsaturation as discussed, supra, to the corresponding amine. This process is preferred because it is considerably more facile when dealing with meta-substituted or halo-substituted phenylacetamide reactants which pose some problems when proceeding through the acetonitrile intermediate. This route to the desired end products also permits one to readily vary the valued R_1 and R_2 in the initial reactant.

The cyano substituent representing R_5 and/or R_6 is introduced after all reduction steps have been completed by displacement of an R_5–R_6 halo substitution with cuprous cyanide. The amino substituents representing R_5 and/or R_6 are protected throughout the reaction sequence with a protecting group such as 1,1,4,4-tetramethyl-1,4-dichlorosilylethylene which completely blocks the amino nitrogen atom from undesireable reactions. After completion of the reaction sequence, the amino group is deprotected and alkylated or acylated by conventional means to provide a mono- or di-alkylamine or an alkanamido group in each case of 1 to 6 carbon atoms. The nitro substituent representing R_5 and/or R_6 is introduced as an aromatic substituent by diazotization of the aromatic amine followed by treatment with alkali metal nitrite in the presence of copper or by formation of the diazonium tetrafluoroborate and reaction with an alkali metal nitrite, thusly:

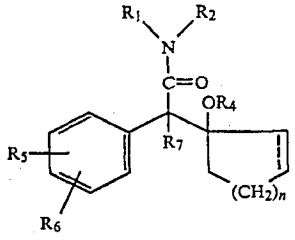






The cyano substituent may be introduced via the diazonium salt with cyprous cyanide in analogous manner.

The intermediate amide represents an additional aspect of this invention and is depicted by the following structural formula:



in which

the dotted line represents optional unsaturation,

R_1 is hydrogen or alkyl of 1 to 6 carbon atoms;

R_2 is alkyl of 1 to 6 carbon atoms;

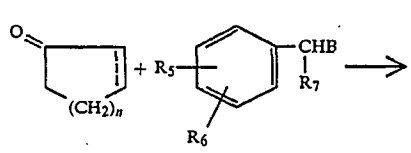
R_4 is hydrogen or alkyl of 1 to 6 carbon atoms;

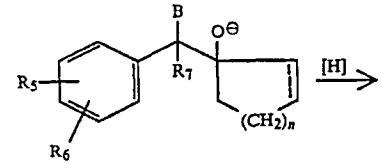
R_5 and R_6 are, independently, hydrogen, hydroxyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, aralkoxy of 7 to 9 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, alkylmercapto of 1 to 6 carbon atoms, N-protected amino, halo, trifluoromethyl, or when taken together, methylenedioxy;

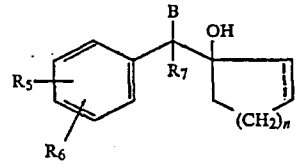
R_7 is hydrogen or alkyl of 1 to 6 carbon atoms; and

n is one of the integers 0, 1, 2, 3 or 4. When R_4 is alkyl it is introduced prior to reduction. The protecting group employed to prevent reaction at the amino substituent representing R_5 and/or R_6 is any protecting group that will completely prevent reaction at a primary $—NH_2$ substituent, such as 1,2-[bis-dimethylsilylchloride]ethane.

More indirect routes for synthesis of the antidepressant compounds of this invention involve the reaction of a cycloalkenone or a cycloalkenone with an anion of an appropriately substituted phenylacetic acid, salt, ester, aldehyde or alcohol

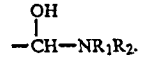






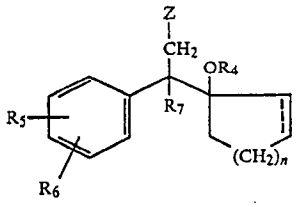
where B represents a carboxyl group or its salt or ester or a —CHO or CH_2OH functional group.

The carboxylic acid group may be converted to an acid halide, active ester or anhydride and directly reacted with the desired amine to yield, after reduction of the resulting amide, the end products of this invention. Also, the carboxylic acid group may be reduced with diisobutyl aluminum hydride or lithium aluminum hydride to obtain the corresponding aldehyde. The ester is readily converted to the aldehyde with diisobutyl aluminum hydride or to the alcohol with lithium aluminum hydride. The aldehyde may be condensed with hydroxylamine to afford the oxime —CH=NOH; with ammonium or a primary amine to afford an imine $—CH=NR_1$ or with a primary or secondary amine to afford

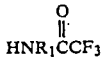


The alcohol $—CH_2OH$ may be converted to the corresponding nitro derivative by producing an organic sulfonate (mesyl ester) or halide followed by displacement with an inorganic nitrite. Reduction of these intermediates yields the primary amine intermediates or the secondary or tertiary amine end products of this invention. The alcohols may be converted to mesylates or tosylates, reacted with KCN to afford the nitrile, converted to the amide and subjected to a Hoffman rearrangement with bromine or chlorine and an alkali metal hydroxide.

Additional routes to the desired products include the reaction of ammonia or HNR_1R_2 with

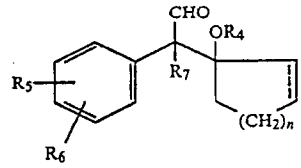


where Z is a leaving group such as a halogen or an organo sulfonyloxy (mesyl, tosyl and the like) group under conventional conditions. If desired, the amine reactant may be initially blocked with a relatively labile acyl group such as trifluoroacetyl to provide a reactant of the formula



prior to reaction with the alkylating reactant employing KOH and a very polar solvent such as dimethylsulfoxide, to provide a tertiary amide from which the acyl group may be readily removed to prepare the compound for non-symmetrical N-alkylation to insert R_2. Rather than N-alkylate, one may acylate or react the secondary amine with an aldehyde and subsequently reduce the amide or Schiff base. Similarly, reaction of the amine with an alkylchloroformate affords, upon reduction, an N-methylated amine. $LiAlH_4$ is a good reducing agent for these processes.

Reductive amination of the aldehyde



with ammonia, a primary amine or a secondary amine (Leuckart reaction) also yields the desired end products.

During the course of the synthesis of the end compounds of the invention by means of processes identified above, any hydroxy group represented by —OR_4, R_5 or R_6 may be in the free form or in the form of hydroxy protected by a removable protecting group, except of course, that the hydroxy group is not protected in any case where it is intended to participate in a reaction. The protected form is recommended where the hydroxy group may otherwise undergo an undesired reaction. Examples of protecting groups for hydroxy are given in Protective Groups in Organic Chemistry edited by J. F. W. McOmie, Chapters 3 and 4 (pages 95–182) published by Plenum Press (1973), and Protective Groups in Organic Chemistry by T. W. Greene, Chapters 2 and 3 (pages 10 to 113) published by John Wiley and Sons (1981). The protecting group may be removed at a suitable later stage in the synthesis. Similarly any amino or alkylamino group may be in a protected form where appropriate during the course of the synthesis of the end compounds. Protecting groups for amino are described in Chapter 2 (pages 43 to 94) of the McOmie book and Chapter 7 (pages 218 to 286) of the Greene book.

The end products contain either one or two asymmetric centers depending upon the saturated and unsaturated state of the cycloaliphatic ring, respectively. Individual stereoisomeric forms may be obtained or separated by standard procedures. For instance separation of the mixture in the case of an amine or carboxylic acid may be carried out by neutralisation with a suitable optically active compound to form salts which can be separated. Example 33 illustrates the typical resolution of the product of Example 3, Compound A.

The antidepressant activity of the end compounds of this invention was established by demonstrating that they (1) inhibit ^{3}H-imipramine binding in brain tissue when tested by a method analogous to that of Raisman et. al., Eur. J. Pharmacol. 61, 373–380 (1980); (2) inhibit synaptosomal uptake of norepinephrine (^{3}H-NE) and serotonin (^{14}C-5-HT) following the test procedure of Wood et. al., J. Neurochem. 37, 795–797 (1981); and antagonize reserpine induced hypothermia when tested in accordance with the procedure of Askew, Life Sci. 1, 725–730 (1963).

The results of these procedures affirmed the antidepressant activity of the end compounds of this invention in agreement with the most widely accepted theory of antidepressant activity and in correlation of activity with known tricyclic antidepressants. In at least two instances, namely, with the dimethylamino product of Example 3, and 4-chloro product in Example 11, the undesirable attribute of classical antidepressants observed as an anticholinergic property which is reflected by the inhibition of binding of the muscarinic receptor ligand, 3H-quinuclidinyl benzilate (QNB), and in the inhibition of carbachol-stimulated contraction of the guinea-pig ileum, is missing. Also missing is the attribute of classical antidepressants observed as an antihistaminic property which is reflected by the inhibition of the H_1 histamine receptor ligand, 3H-pyrilamine, and in the inhibition of histamine-stimulated contraction of the guinea-pig ileum.

As representative examples of the activity profile of the end compounds of this invention, the following data for testing of the dimethylamino product of Example 3, hereinafter Compound A, its oxazine variant, hereinafter Compound B, the 4-chloro product of Example 11, hereinafter referred to as Compound C, the 4-bromo product of Example 15, hereinafter referred to as Compound D, the 3-chloro product of Example 17, hereinafter referred to as Compound E, the 3-bromo product of Example 16, hereinafter referred to as Compound F, and the 3,4-dichloro product of Example 19, hereinafter referred to as Compound G, are presented as follows:

Inhibition of ^{3}H-imipramine binding: Compound A (HCl Salt) exhibited an inhibition constant (K_i) vs. ^{3}H-imipramine of 90 nM, making it a fairly potent ligand at this receptor site. Compound B was somewhat less potent, with a K_i of 350 nM. Compound C was virtually equipotent with Compound A, exhibiting a K_i vs. ^{3}H-imipramine of 100 nM. While not as potent as imipramine (K_i=1.7 nM), these values fall in the range of desmethylimipramine (DMI) (K_i=130 nM) and other tricyclic antidepressants. Atypical antidepressants (non-tricyclic) which have been tested, exhibit K_i's greater than 5000 nM in this assay. Compounds D, E, F and G exhibited inhibition constants of 62, 130, 52 and 37, respectively. Compounds A through G, representative of the other compounds of this invention, are thus comparable to known tricyclic antidepressants in this test.

Inhibition of synaptosomal NE and 5-HT uptake: Results of the inhibition of NE and 5-HT synaptosomal uptake, expressed as the inhibitory concentration at which the rate of uptake was reduced to 50 percent (IC_{50}), are presented in the table below, where they are compared with the values for imipramine, DMI and amitriptyline:

Compound	IC_{50} (μM) NE	5-HT
Imipramine	0.26	0.12
DMI	0.15	3.0
Amitriptyline	0.50	0.60
Compound A	0.64	0.21
Compound B	4.7	2.9
Compound C	0.33	0.25
Compound D	0.21	0.11
Compound E	0.16	0.32
Compound F	0.11	0.23
Compound G	0.07	0.08

These results show that Compounds A and C to G are approximately equipotent to imipramine in NE and 5-HT uptake inhibition. Again, Compound B is somewhat less potent.

Inhibition of ^{3}H-QNB binding: In the QNB receptor binding assay, the Compounds A and C–G exhibited an IC_{50} greater than 10^{-5} molar and were therefore essentially inactive. Imipramine and DMI exhibit K_i's of 37 nM and 50 nM, respectively. These results suggest that, unlike the tricyclic antidepressants, Compounds A and C–G would have no muscarinic anticholinergic actions.

Inhibition of Carbachol-stimulated contraction of guinea-pig ileum: While imipramine at 1 μM exhibits a K_B of approximately 100 nM against carbachol-stimulated contraction of the guinea-pig ileum, Compound A was inactive at 1 μM. This result supports the suggestion of a lack of muscarinic anticholinergic action of Compound A.

Inhibition of ^{3}H-pyrilamine binding: While DMI exhibits a K_i versus ^{3}H-pyrilamine binding of 124 nM, Compound A was inactive. Compounds D–G exhibited an IC_{50} greater than 10^{-5} molar. These results suggest that, unlike tricyclic antidepressants, Compounds A and D–G have no antihistaminic property.

Inhibition of histamine-stimulated contraction of the guinea-pig ileum: Imipramine at 1 μM inhibits the histamine-stimulated contraction of the guinea-pig ileum with an approximate K_B of 8 nM. Compound A, in contrast, had no effect in this test at a concentration of 1 μM. This result supports the notion that Compound A has no antihistaminic action.

Antagonism of reserpine-induced hypothermia: The minimum effective dosage (M.E.D.) of compounds A through G established in antagonism of reserpine-induced hypothermia in mice (n=8 per group) in relation to desmethylimipramine (DMI) were:

Compound	Dose, mg/kg, i.p.
DMI	0.4
A	10.0 (and p.o.)
B	30.0
C	10.0
D	3.0
E	1.0
F	1.0
G	3.0

All mice received 5 mg/kg reserpine s.c. 18 h prior to test compound.

DMI, and Compounds A to G, are of approximately equal efficacy in the reversal of reserpine-induced hypothermia. Compound B was less potent than Compound A, Compound C was approximately equipotent with Compound A, Compounds D and G were approximately three times as potent as Compound A, and Compounds E and F were approximately ten times as potent as Compound A in the study.

Hence, the end compounds of this invention are useful in the treatment of depression, for which purpose they may be administered orally or parenterally in an amount sufficient to alleviate the symptoms of depression. The actual amount of antidepressant agent to be used will vary with the severity and nature of the depressed state, the animal being treated and the level of relief sought. In the human, an oral dose of from about 2 to about 50 milligrams, administered as needed represents appropriate posology. Intramuscular administration of from about 1 to about 25 milligrams provides a dosage comparable to that specified for oral administration. As with other antidepressants, therapy should be initiated with lower dosages and increased until the desired symptomatic relief is obtained.

Pharmaceutical compositions containing the antidepressant compounds of this invention represent an additional aspect of this invention. The active ingredient can be compounded into any of the usual oral dosage forms including tablets, capsules and liquid preparations such as elixirs and suspensions containing various colouring, flavouring, stabilizing and flavour masking substances. For compounding oral dosage forms, the active ingredient can be mixed with various conventional tabletting materials such as starch, calcium carbonate, lactose, sucrose and dicalcium phosphate to aid the tabletting or capsulating process. Magnesium stearate, as an additive, provides a useful lubricant function when desired.

The active ingredients can be dissolved or suspended in a pharmaceutically acceptable sterile liquid carrier, such as sterile water, sterile organic solvent or a mixture of both. Preferably a liquid carrier is one suitable for parenteral injection. Where the active ingredient is sufficiently soluble it can be dissolved in normal saline as a carrier; if it is too insoluble for this it can often be dissolved in a suitable organic solvent, for instance aqueous propylene glycol or polyethylene glycol solutions. Aqueous propylene glycol containing from 10 to 75% of the glycol by weight is generally suitable. In other instances other compositions can be made by dispersing the finely-divided active ingredient in aqueous starch or sodium carboxymethyl cellulose solution, or in a suitable oil, for instance arachis oil. Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by intramuscular, intraperitoneal or subcutaneous injection.

Preferably the pharmaceutical composition is in unit dosage form, e.g. as tablets or capsules. In such form, the composition is sub-divided in unit doses containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example, packeted powders or vials or ampoules. The unit dosage form can be a capsule, cachet or tablet itself, or

it can be the appropriate number of any of these in package form. The quantity of the active ingredient in a unit dose of composition may be varied or adjusted from 2 mg. or less to 50 mg. or more, according to the particular need and the activity of the active ingredient.

The following examples illustrate the preparative technique employed in production of the compounds of the invention.

EXAMPLE 1

1-[Cyano(p-methoxyphenyl)methyl]cyclohexanol

p-Methoxyphenylacetonitrile (50 gm, 0.3 mole) was added to dry tetrahydrofuran (250 ml) and the solution cooled to −70° C. under nitrogen. n-Butyl lithium in hexane (210 ml, 0.3 mole) was added dropwise, with stirring. The temperature was maintained below −50° C. and a yellow precipitate appeared. After the addition was complete, the reaction mixture was maintained below −50° C. for 30 minutes and cyclohexanone (35 ml, 0.3 mole) was added. After a further 45 minutes below −50° C. the temperature was allowed to rise to 0° C. and a saturated ammonium chloride solution was added. The layers were separated and the aqueous layer extracted with diethyl ether. The combined organic solution was washed with brine, dried over magnesium sulphate and evaporated. The product crystallized (25.2 gm, m.p. 125°–127° C.).

Mass Spectral Analysis: Molecular weight 245 [(M+1)+ by C.I.M.S.]

N.M.R. Analysis: δ 7.32, 6.95; (4H quartet, p-substituted aromatic) 3.8 (3H singlet, O—CH_3); 3.76 (1H, singlet, CH—CN); 1.56 (10H, multiplet, aliphatic cyclohexyl)ppm.

EXAMPLE 2

1-[2-amino-1-(p-methoxyphenyl)ethyl]cyclohexanol

1-[cyano(p-methoxyphenyl)methyl]cyclohexanol (12 g, 0.05 mole) was dissolved on warming in a mixture of ammonia-ethanol (20% v/v, 250 ml) and hydrogenated in a Parr apparatus over 5% rhodium on alumina (2.8 gm). The catalyst was filtered, washed well with ethanol and the combined filtrate evaporated and dried under vacuum yielding an oil (12 gm).

Mass Spectral Analysis: Molecular weight 249 (M+1)+ by C.I.M.S.

Thin Layer Chromatography: single spot, ninhydrin positive [chloroform-methanol-acetic acid (80:10:10 v/v)].

EXAMPLE 3

5-(4-methoxyphenyl)-3-methyl-3-aza-1-oxaspiro(5.5)-undecane and
1-[2-dimethyl-amino)-1-(4-methoxyphenyl)ethyl]cyclohexanol

1-[2-amino-1-(p-methoxyphenyl)ethyl]cyclohexanol (12 gm; 0.048 mole) was treated with a mixture of formaldehyde (11 ml), formic acid (14.5 ml, 88%) and water (125 ml) and heated at 100° C. for five hours. The reaction mixture was cooled and extracted with ethyl acetate. This extract was discarded. The aqueous residue was cooled in ice, rendered basic by the addition of solid potassium hydroxide, saturated with sodium chloride and thrice extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous potassium carbonate and evaporated to an oily residue (8 gm). This mixture of products was chromatographed on 1 kg of Mallinckrodt Silicar CC7 silica gel and the progress of the chromatography was monitored by thin layer chromatography using a system comprising ethanol:2N ammonia:ethyl acetate:cyclohexane 45:8:100:100 (v/v). Fractions containing the desired products were combined and the hydrochloride salts prepared using 4-N-isopropanolic HCl. The yields of the free bases were 1.4 gm (spiro compound) and 4.6 gm (dimethylamine) respectively.

COMPOUND B

5-(4-methoxyphenyl)-3-methyl-3-aza-1-oxaspiro(5.5)undecane

Melting Point: 242°–244° C.

Mass Spectral Analysis: Molecular weight 275 (M+1)+ by C.I.M.S.

N.M.R. Analysis: δ 7.22, 6.96 (4H quartet, p-substituted aromatic) 4.78 (2H quartet, O—CH_2—NCH_3) 3.8 (4H, O—CH_3, CH—CH_2—NCH_3) 3.3 (2H, multiplet CH—CH_2—NCH_3) 2.8 (3H, NCH_3) 0.9–1.8 (10H, broad multiplet, aliphatic cyclohexyl)ppm.

Compound A

1-[(2-dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol.

The hydrochloride: m.p. 215°–217° C.

Mass Spectral Analysis: Molecular weight 279 (M+1)+ by C.I.M.S. (free base).

N.M.R. Analysis: δ 7.32, 6.98 (4H quartet, p-substituted aromatic) 3.78 (3H, O—CH_3) 3.64 (2H, multiplet $CH_2N(CH_3)_2$) 3.06 (1H, multiplet CH—$CH_2(NCH_3)_2$) 2.74 (6H, $N(CH_3)_2$) 1.38 (10H, broad multiplet, alphatic cyclohexyl)ppm.

EXAMPLE 4

1-[1-(4-methoxyphenyl)-2-dimethylaminoethyl]cyclohexene

8.0 grams (0.029 moles) of 1-[1-(4-methoxyphenyl)-2-dimethylaminoethyl]cyclohexanol was dissolved in 300 ml of 2.0N aqueous hydrochloric acid and heated at reflux for 18 hours. It was allowed to cool, neutralized with 15% aqueous sodium hydroxide and extracted with chloroform. The chloroform extract was dried over sodium sulfate, filtered, and concentrated in vacuo to yield 7.0 grams of solid. This material was converted to the hydrochloride salt by treatment with 5N isopropanolic HCl and recrystallized a second time from isopropanol to yield 2.0 grams of the title compound as a white solid hydrochloride salt, m.p. 187°–189° C.

Analysis for: $C_{17}H_{26}ONCl$: Calculated: C, 69.23; H, 8.91; N, 4.75. Found: C, 69.39; H, 8.95; N, 4.95.

EXAMPLE 5

1-[(α-Aminomethyl)benzyl]-cyclohexanol

Phenylacetonitrile (10 g, 0.08 mole) was added to dry THF (100 ml) and the solution cooled to −70° C. under nitrogen. n-Butyllithium in hexane (64 ml, 0.1 mole) was added dropwise, the temperature being maintained below −40° C. and a yellow precipitate appeared. After addition the reaction mixture was maintained near −70° C. for 30 minutes and cyclohexanone (10 g, 0.1 mole) was added. After a further 45 minutes at −70° C. the temperature was allowed to rise to 0° C. and saturated ammonium chloride solution was added. The layers were separated and the aqueous layer extracted with diethyl ether. The combined organic solution was washed with brine, dried over magnesium sulphate and

evaporated. The product, 1-[α-cyanobenzyl]-cyclohexanol, crystallized (4.93 g, m.p. 100°–102° C.).

Mass Spectral Analysis: Molecular weight 215 (M+).

N.M.R. Analysis: δ 7.4 (5H singlet, aromatic 3.8 (1H, singlet, CH—CN) 1.6 (10H, multiplet aliphatic cyclohexyl)ppm.

A solution of 1-(α-cyanobenzyl)cyclohexanol (3.43 g, 0.02 mole) in a mixture of methanol and ammonia (9:1 v/v, 60 ml) was hydrogenated in a Parr apparatus over 5% rhodium on alumina (2 g). The catalyst was filtered and the filtrate evaporated. The residue was dissolved in ethyl acetate, washed with brine, dried over magnesium sulfate and evaporated. The hydrochloride m.p. 220°–222° (1.2 g) crystallized from diethyl ether-acetone.

Analysis for: $C_{14}H_{21}NO.HCl$: Calculated: C, 64.29; H, 8.67; N, 5.47%. Found: C, 65.74; H, 8.51; N, 5.56%.

N.M.R. Analysis (DMSO) δ 7.73 (5H singlet, aromatic) 3.46 (2H multiplet CH_2—NH_2), 3.0 (1H multiplet CH—CH_2NH_2) 0.9–1.7 (10H multiplet-aliphatic cyclohexyl) ppm.

Mass Spectral Analysis by Chemical Ionization: 220 (M+H)+ (Mol. Wt. 219) (free base).

EXAMPLE 6

1-(α-[(Dimethylamino)methyl]benzyl)-cyclohexanol

1-[α-(aminomethyl)benzyl]cyclohexanol (1.38 g, 0.006 mole) was dissolved in a mixture of formaldehyde (2 ml) formic acid (2.6 ml) and water (25 ml), and refluxed at 95° C. for 18 hours. The reaction mixture was cooled, basified with solid KOH and extracted with methylene chloride. The extract was washed with brine, dried over magnesium sulphate and evaporated. The hydrochloride (m.p. 225°–227° C.) was prepared using 3N-isopropanolic HCl. Yield 589 mg.

Analysis for: $C_{16}H_{25}NO.HCl$: Calculated: C, 67.36; H, 9.12; N, 4.88%. Found: C, 67.7; H, 9.23; N, 4.93%.

Mass Spectral Analysis: Molecular weight 247 (M+, *free base*).

N.M.R. analysis: (DMSO) δ 7.4 (5H singlet, aromatic), 3.68 (2H, multiplet CH_2—N $(CH_3)_2$, 3.18 (1H, multiplet CH—CH_2N—$(CH_3)_2$ 2.68 (6H, $N(CH_3)_2$; 0.9–1.7 (10H multiplet aliphatic cyclohexyl)ppm.

EXAMPLE 7

1-(α-[(Methylamino)methyl]benzyl)cyclohexanol

1-[α-(aminomethyl)benzyl]cyclohexanol (1.59 g., 0.007 (mole) was dissolved in diethyl ether (10 ml.) and cooled to 5° C. Trifluoroacetic anhydride (2 g) was added and the mixture stirred at 0° C. for 30 minutes. The mixture was neutralized using saturated sodium bicarbonate solution and the layers separated. The organic layer was washed with brine, dried over magnesium sulphate and evaporated. A crystalline trifluoroacetamide m.p. 78°–80° C. was obtained (975 mg.).

The trifluoroacetamide (975 mg.) was dissolved in dry acetone (20 ml.) and treated with methyl iodide (2 g.). The solution was warmed to reflux temperature and dry powdered potassium hydroxide (1 g.) added, followed by excess methyl iodide. The mixture was refluxed for five minutes, then cooled and the acetone evaporated. Water (20 ml.) was added and the mixture refluxed for 15 minutes. It was cooled and extracted with ethyl acetate. The extract was washed with water and brine, dried over magnesium sulfate and evaporated to a crystalline product m.p. 92°–94° C. This was converted to the hydrochloride using 3N-isopropanolic HCl. Yield 235 mg., m.p. 208°–210° C.

N.M.R. Analysis ($CHCl_3$), δ 7.3 (7H, aromatic, HCl and NH.CH_3); 3.9 (1H multiplet CH—CH_2NH_2); 3.25 (2H multiplet CH_2—NH_2); 2.6 (3H singlet NH—CH_3); 0.8–1.9 (10H multiplet, aliphatic cyclohexyl)ppm.

Mass Spectral Analysis: Molecular weight by chemical ionization/M.S. 233 (M+1 at 234, free base).

EXAMPLE 8

1-(α-[(Dimethylamino)methyl]benzyl)cyclohexanol acetate

1-(α-[(Dimethylamino)methyl]benzyl)cyclohexanol, (0.5 g., 0.0025 mole) was treated with acetic anhydride (1 ml.) and pyridine (3 ml.) and the mixture stood at room temperature overnight. The reaction mixture was poured into water, basified with solid KOH and extracted with ethyl acetate. The extract was washed with water and brine, dried over magnesium sulphate and evaporated to an oil. After azetropic distillation with toluene to remove traces of pyridine, the oil was treated with 3N isopropanolic HCl and crystalline hydrochloride as the title compound was obtained (70 mg.) m.p. 163°–165° C.

NMR Analysis: ($CHCl_3$) δ 7.35 (5H singlet, aromatic); 4.2 (1H multiplet $CHCH_2N(CH_3)2$; 3.6 (2H multiplet CH_2—$N(CH_3)_2$); 2.65 (6H singlet, $N(CH_3)_2$); 2.1 (3H singlet, —O—C—CH_3): 0.9–1.7 (10H multiplet, aliphatic cyclohexyl)ppm.

Mass Spectral Analysis: Molecular weight 289 (M+, free base).

EXAMPLE 9

1-[cyano(p-chlorophenyl)methyl]cyclohexanol

By replacing the p-methoxyphenyl acetonitrile in Example 1 by a molar equivalent amount of p-chlorophenyl acetonitrile, there was obtained 1-cyano(p-chlorophenyl)methyl cyclohexanol (13.7 g.) m.p. 115°–117°.

Mass Spectral Analysis: Molecular weight 249 (M+1)+ by C.I.M.S.

EXAMPLE 10

1-[2-amino-1-(4-chlorophenyl)ethyl]cyclohexanol

Lithium aluminum hydride (3.5 g.) was suspended in ice cold tetrahydrofuran (125 ml.) and concentrated sulphuric acid (2.5 ml.) added cautiously, with stirring. After one hour, 1-[cyano(p-chlorophenyl)methyl]cyclohexanol (15 g., 0.06 mole) was dissolved in tetrahydrofuran (100 ml.) and added rapidly dropwise with vigorous stirring and cooling. After a further two hours, a tetrahydrofuran-water mixture (1:1; 30 ml.) was added followed by 10% sodium hydroxide solution (50 ml.). The tetrahydrofuran was decanted and the residue washed well with diethyl ether and ethylacetate. The combined organic solution was dried over anhydrous potassium carbonate and evaporated to an oil (12 g.)

Mass Spectral Analysis: Molecular weight 253 (M+1)+ by C.I.M.S.

EXAMPLE 11

1-[1-(4-chlorophenyl)-2-(dimethylamino)ethyl]cyclohexanol

1-[2-amino-1-(4-chlorophenyl)ethyl]cyclohexanol (12 g., 0.04 mole) was treated with a mixture of formaldehyde (13.7 ml.) formic acid (18.1 ml.) and water (160

ml.) and refluxed at 100° C. for four hours. The reaction mixture was cooled extracted well with ethyl acetate and the extract discarded. The aqueous residue was cooled in ice and rendered basic by the addition of solid potassium hydroxide, saturated with sodium chloride and thrice extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous potassium carbonate and evaporated. A crystalline solid (3 g.) was filtered. It was converted to the hydrochloride salt using 4N-isopropanolic HCl; yielding 4.7 g., m.p. 241°–243° C.

Mass Spectral Analysis: Molecular Weight 281 $(M+1)^+$ by C.I.M.S.

NMR Analysis: δ 7.35 (4H singlet characteristic of 4chloro substitution) 3.65 (2H multiplet, CH_2—$CHN(CH_3)_2$), 3.0 (1H multiplet $CH_2CHN(CH_3)_2$ 1.4 (10H multiplet, aliphatic cyclohexyl)ppm.

EXAMPLE 12

1-[1-(4-methoxyphenyl)-2-(methylamino)ethyl]cyclohexanol

By replacing 1-[α-(aminomethyl)benzyl]cyclohexanol with a molar equivalent amount of 1-[2-amino-1-(p-methoxyphenyl)ethyl]cyclohexanol in Example 7, 1-[1-(4-methoxyphenyl)-2-methylamino)ethyl]cyclohexanol hydrochloride (m.p. 164°–166° C.) was obtained.

Mass Spectral Analysis: Molecular Weight 263 $(M+1)^+$ by C.I.M.S.

NMR Analysis: δ 7.28, 6.92 (4H quartet, p-substituted aromatic) 3.76 (3H singlet, OMe) 3.4 (2H multiplet, CH_2—$CHNCH_3)_2$ 2.9 (1H multiplet, $CH_2CHN(CH_3)_2$) 2.54 (3H, NCH_3) 1.4 (10H broad multiplet, aliphatic cyclohexyl)ppm.

EXAMPLE 13

4-bromo-N,N-dimethylbenzene acetamide

Para-bromophenylacetic acid (50 g., 0.233 mole) was dissolved in methylene chloride (500 ml) and treated with oxalyl chloride (23.3 ml., 0.27 mole) and D.M.F. (0.5 ml) at room temperature. The mixture was stirred for four hours until gas evolution ceased. The solvent was evaporated and the residue dried under vacuum to remove excess oxalyl chloride. The residue was dissolved in methylene chloride (300 ml) and treated with an excess of gaseous dimethylamine. The mixture was stirred overnight and the solvent evaporated. The residue was redissolved in methylene chloride and the solution washed with saturated sodium bicarbonate solution, N-hydrochloric acid, water, brine, dried over magnesium sulphate and evaporated. The buff-colored crystals were filtered with hexane and air-dried. Yield 51.2 g., m.p. 73°–76° C.

Analysis for: $C_{10}H_{12}NOBr$: Calculated: C, 49.59; H, 4.96; N, 5.79. Found: C, 48.98; H, 5.14; N, 5.77.

NMR Analysis ($CHCl_3$): δ 7.55 (4H quartet, aromatic) 3.65 (2H singlet) 2.95 (6H singlet, $N(CH_3)_2$)ppm.

EXAMPLE 14

1-[(4-bromophenyl)[(dimethylamino)carbonyl]methyl]-cyclohexanol

4-bromo-N,N-dimethylbenzene acetamide (15 g., 0.06 mole) was added to dry T.H.F. (250 ml) and the solution cooled to −78° C. under nitrogen. Straight chain butyl lithium in hexane (43.3 ml, 0.06 mole) was added dropwise, the temperature being maintained below −70° C. throughout. An orange coloured precipitate formed. After addition, the reaction mixture was maintained near −70° C. for 20 minutes and cyclohexanone (7.5 ml, 0.07 mole) was added. After a further 50 minutes at −78° C. the reaction mixture was poured into stirring saturated ammonium chloride solution. The layers were separated and the aqueous layer extracted with diethyl ether. The combined organic solution was washed with brine, dried over magnesium sulfate and evaporated. The product crystallised and was filtered with isopropanol (9.8 g., m.p. 140°–144° C.).

Analysis for: $C_{16}H_{22}NO_2Br$: Calculated: C, 56.47; H, 6.47; N, 4.12. Found: C, 57.22; H, 6.66; N, 4.21.

NMR Analysis ($CHCl_3$) δ 7.35 (4H, aromatic) 3.63 (1H singlet CH—$CON(CH_3)_2$) 2.95 (6H singlet, N—$(CH_3)_2$); 1.45 (10H multiplet, aliphatic cyclohexyl)ppm.

EXAMPLE 15

1-[1-(4-bromophenyl)-2-(dimethylamino)ethyl]cyclohexanol

Lithium aluminum hydride (0.7 g.) was suspended in dry THF (25 ml) cooled to 0° C. and concentrated sulfuric acid (0.5 ml) cautiously added in an in situ preparation of aluminum hydride. The mixture was stirred for one hour at 0° C. and the amide, 1-[(4-bromophenyl)[dimethylaminocarbonyl]methyl]cyclohexanol (4 g., 0.012 mole) was dissolved in THF (35 ml) and added rapidly dropwise. The reaction mixture was stirred at 0° C. for one hour. A THF-water mixture (1:1 v/v 6 ml) was added slowly followed by 10% sodium hydroxide (10 ml). The mixture was filtered and the residue washed well with ethyl acetate. The combined filtrate was dried over anhydrous potassium carbonate and evaporated to an oil (3.5 g) which was converted to the hydrochloride salt using 4N isopropanolic HCl.

Analysis for: $C_{16}H_{24}NOBr.HCl$: Calculated: C, 52.97; H, 6,9; N, 3.86. Found: C, 52.71; H, 6.63; N, 3.71.

NMR Analysis: (DMSO): δ 7.4 (4H, aromatic) 3.55 (2H doublet CH—$CH_2N(CH_3)_2$); 3.05 (1H, triplet, CH—$CH_2N(CH_3)_2$); 2.63 (6H singlet, N—$(CH_3)_2$) 1.30 (10H multiplet, aliphatic cyclohexyl)ppm.

EXAMPLE 16

1-[1-(3-bromophenyl)-2-dimethylamino)ethyl]cyclohexanol

By replacing p-bromophenyl acetic acid with a molar equivalent amount of m-bromophenyl acetic acid in Example 13, and following procedures described in Examples 14 and 15, 1-[1-(3-bromophenyl)-2-(dimethylamino)ethyl]cyclohexanol was obtained as the hydrochloride, m.p. 198°–201° C.

Analysis for: $C_{16}H_{24}NOBr.HCl$: Calculated: C, 52.97; H, 6.90; N, 3,86. Found: C, 52.84; H, 6.92; N, 3.99.

EXAMPLE 17

1-[1-(3-chlorophenyl)-2-(dimethylamino)ethyl]cyclohexanol

By replacing p-bromophenyl acetic acid with a molar equivalent amount of m-chlorophenylacetic acid in Example 13, and following procedures described in Examples 14 and 15, 1-[1-(3-chlorophenyl)-2-(dimethylamino)ethyl]cyclohexanol was obtained as the hydrochloride, m.p. 214°–216° C.

Analysis for: $C_{16}H_{24}NOCl.HCl$: Calculated: C, 60.38; H, 7.86; N, 4.4. Found: C, 60.07; H, 7.79; N, 3.93.

EXAMPLE 18

1-[1-(2-chlorophenyl)-2-(dimethylamino)ethyl]cyclohexanol

By replacing p-bromophenyl acetic acid with a molar equivalent amount of o-chlorophenylacetic acid in Example 13, and following procedures described in Examples 14 and 15, 1-[1-(2-chlorophenyl)-2-(dimethylamino)ethyl]cyclohexanol was obtained as the hydrochloride, m.p. 205°–206° C.

Analysis for: $C_{16}H_{24}NOCl.HCl$: Calculated: C, 60.38; H, 7.86; N, 4.4. Found: C, 60.45; H, 7.71; N, 4.79.

EXAMPLE 19

1-[1-(3,4-dichlorophenyl)-2-(dimethylamino)ethyl]cyclohexanol

By replacing p-bromophenyl acetic acid with a molar equivalent amount of 3,4-dichlorophenylacetic acid in Example 13, and following procedures described in Examples 14 and 15, 1-[1-(3,4-dichlorophenyl-2-(dimethylamino)ethyl]cyclohexanol was obtained as the hydrochloride, m.p. 241°–244° C.

Analysis for: $C_{16}H_{23}NOCl_2.HCl$: Calculated: C, 54.47; H, 6.81; N, 3.97. Found: C, 54.8; H, 6.83; N, 3.99.

EXAMPLE 20

1-[1-(3,4-dichlorophenyl-2-(dimethylamino)ethyl]cyclohexanol

The product of the preceding example is similarly produced by the following procedure:

Lithium diisopropylamide was prepared by dissolving di-isopropylamine (69 ml) in THF (500 ml) followed by the addition of n-butyllithium (325 ml). After 10 minutes stirring, the straw colored liquid was cooled to −78° C. and a solution of the 3,4-dichloro-N,N-dimethylbenzeneacetamide (110.9 g, crude) was dissolved in 300 ml THF and added slowly. A dark red slurry was obtained. The mixture was stirred for a further 20 minutes and cyclohexanone (55.7 ml) was added. After 60 minutes at −78° C. the reaction mixture was poured into a saturated solution of ammonium chloride. The aqueous layer was extracted with diethyl ether and the combined organic solution was washed with brine, dried over K_2CO_3 and evaporated. The product, 1-[(3,4-dichlorophenyl) (dimethylaminocarbonyl)methyl]cyclohexanol, crystallized and was filtered. The crystals were washed with isopropanol and with petroleum ether and air dried. Yield: 73.6 g., m.p. 118°–120° C.

To an ice cold solution of Borane THF complex (152 ml, 152 mmole) was added a solution of 1-[(3,4-dichlorophenyl)(dimethylaminocarbonyl)methyl]cyclohexanol (30 g, 90 mmole) in THF. The mixture was refluxed for 2 hours and cooled again in an ice bath. 2N HCl (23 ml) was added and the mixture refluxed for 1.5 hours. It was cooled overnight. The reaction mixture was basified to pH 14 with solid potassium hydroxide and the layers were separated. The organic layer was washed with brine, dried over magnesium sulfate and evaporated to a solid. This was filtered and washed with diethyl ether and air dried. Yield: 15.4 g.; m.p. 128°–130° C.

This product was converted to the hydrochloride which was identical with the product in Example 19.

EXAMPLE 21

1-[2-(dimethylamino)-1-(3-methoxyphenyl)ethyl]cyclohexanol

By replacing p-bromophenyl acetic acid with a molar equivalent amount of m-methoxyphenyl acetic acid in Example 13, and following procedures described in Examples 14 and 15, 1-[2-(dimethylamino)-1-(3-methoxyphenyl)ethyl]cyclohexanol was obtained as the hydrochloride, m.p. 166°–168° C.

Analysis for: $C_{16}H_{25}NO_2.HCl$: Calculated: C, 64.11; H, 8.68; N, 4.67. Found: C, 63.12; H, 8.54; N, 4.46.

EXAMPLE 22

1-[1-(3,4-dimethoxyphenyl)-2-(dimethylamino)ethyl]-cyclohexanol

By replacing p-bromophenyl acetic acid with a molar equivalent amount of 3,4-dimethoxyphenyl acetic acid in Example 13, and following procedures described in Examples 14 and 15, 1-[1-(3,4-dimethoxyphenyl)-2-(dimethylamino)ethyl]cyclohexanol was obtained as the hydrochloride.

Analysis for: $C_{18}H_{29}NO_3.HCl$: Calculated: C, 62.88; H, 8.74; N, 4.08. Found: C, 62.42; H, 8.56; N, 3.98.

EXAMPLE 23

1-[2-(dimethylamino)-1-(4-trifluoromethylphenyl)ethyl]cyclohexanol

By replacing p-bromophenyl acetic acid with a molar equivalent amount of p-trifluoromethylphenyl acetic acid in Example 13, and following procedures described in Examples 14 and 15, 1-[2-(dimethylamino)-1-(4trifluoromethylphenyl)ethyl]cyclohexanol was obtained as the hydrochloride, m.p. 238°–240° C.

Analysis for: $C_{17}H_{25}NOF_3.HCl$: Calculated: C, 58.03; H, 7.16; N, 3.98. Found: C, 58.47; H, 7.16; N, 4.07.

EXAMPLE 24

1-[2-(dimethylamino)-1-(3-trifluoromethylphenyl)ethyl]cyclohexanol

By replacing p-bromophenyl acetic acid with a molar equivalent amount of m-trifluoromethylphenyl acetic acid in Example 13, and following procedures described in Examples 14 and 15, 1-[2-(dimethylamino)-1-(3-trifluoromethylphenyl)ethyl]cyclohexanol was produced as the hydrochloride, m.p. 194°–196° C.

Analysis for: $C_{17}H_{25}NOF_3.HCl$: Calculated: C, 58.03; H, 7.16; N, 3.98. Found: C, 58.31; H, 7.09; N, 4.09.

EXAMPLE 25

1-[2-(dimethylamino)-1-(4-methylphenyl)ethyl]cyclohexanol

By replacing p-bromophenyl acetic acid with a molar equivalent amount of p-methylphenyl acetic acid in Example 13, and following procedures described in Examples 14 and 15, 1-[2-(dimethylamino)-1-(4-methylphenyl)ethyl]cyclohexanol was produced as the hydrochloride.

Analysis for: $C_{17}H_{17}NO.HCl$: Calculated: C, 68.54; H, 9.17; N, 4.70. Found: C, 68.37; H, 9.31; N, 4.83.

EXAMPLE 26

1-[2-(dimethylamino)-1-(4-hydroxyphenyl)ethyl]cyclohexanol

By replacing p-bromophenyl acetic acid with a molar equivalent amount of p-benzyloxyphenyl acetic acid in Example 13, and following the procedures described in Examples 14 and 15, 1-[1-(4-benzyloxyphenyl)-2-(dimethylamino)ethyl]cyclohexanol was obtained.

Hydrogenolysis of this product to remove the benzyl protecting group from the 4-hydroxyphenyl moiety was accomplished by dissolving 1.0 grams of the product in 100 ml. ethanol. One gram, 10% Pd/C was introduced followed by cyclohexa-1,4-dienone (5 ml.). The mixture was stirred for ninety minutes at ambient temperature. The catalyst was removed by filtration and the solvent removed by evaporation to yield 800 mg. of solid. This solid 4-hydroxyphenyl product was converted to its fumarate salt via an acetone-ethanol solution, m.p. 140°–142° C.

Analysis for: $C_{16}H_{25}NO_2.C_4H_4O_4$: Calculated: C, 63.30; H, 7.70; N, 3.69. Found: C, 62.18; H, 7.90; N, 3.63.

EXAMPLE 27

1-[2-(dimethylamino)-1-(3-hydroxyphenyl)ethyl]cyclohexanol

By replacing p-bromophenyl acetic acid with a molar equivalent amount of m-benzyloxyphenyl acetic acid in Example 13, and following the procedures described in Examples 14 and 15, 1-[1-(3-benzyloxyphenyl)-2-(dimethylamino)ethyl]cyclohexanol was obtained.

Hydrogenolysis of this product (2.3 g) was conducted in 200 ml ethanol employing a Paar bomb, 300 mg. 10% Pd/C until uptake of hydrogen ceased. The catalyst was removed by filtration and the solvent evaporated to afford a solid product which was converted to its hydrochloride salt with 5N isopropanolic hydrochloride, m.p. 162°–164° C.

Analysis for: $C_{16}H_{25}NO_2.HCl$: Calculated: C, 64.08; H, 8.74; N, 4.67. Found: C, 62.78; H, 8.55; N, 4.55.

EXAMPLE 28

1-[1-(4-bromophenyl)-2-(dimethylamino)ethyl]cyclobutanol

By replacing cyclohexanone in Example 14 with a molar equivalent amount of cyclobutanone and following the procedure described in Example 15, 1-[1-(4-bromophenyl)-2-(dimethylamino)ethyl]cyclobutanol was obtained. It was converted to the hydrochloride salt, m.p. 220°–222° C.

Analysis for: $C_{14}H_{20}NOBr.HCl$: Calculated: C, 50.22; H, 6.28; N, 4.19. Found: C, 50.26; H, 6.11; N, 4.13.

EXAMPLE 29

1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclopentanol

By replacing p-bromophenylacetic acid with a molar equivalent amount of p-methoxyphenyl acetic acid in Example 13, 4-methoxy-N,N-dimethylbenzene acetamide was obtained. Subsequently, following the procedure outlined in Example 14, replacing cyclohexanone with a molar equivalent amount of cyclopentanone, there was obtained the corresponding cyclopentanol derivative. This intermediate was converted, following the procedure described in Example 15, to the title compound as the hydrochloride, m.p. 194° C.

Analysis for: $C_{16}H_{25}NO_2.HCl$: Calculated: C, 64.07; H, 8.76; N, 4.67. Found: C, 64.19; H, 8.72; N, 4.33.

EXAMPLE 30

1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cycloheptanol

By replacing cyclopentanone with a molar equivalent of cycloheptanone in Example 27, the title compound was obtained as the hydrochloride, m.p. 175°–177° C.

Analysis for: $C_{18}H_{29}NO_2.HCl.\frac{1}{4}H_2O$: Calculated: C, 65.03; H, 9.26; N, 4.21. Found: C, 65.25; H, 9.16; N, 4.29.

EXAMPLE 31

1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclooctanol

By replacing cyclopentanone with a molar equivalent amount of cyclooctanone in Example 29, the title compound was obtained as the hydrochloride, m.p. 178°–180° C.

Analysis for: $C_{19}H_{31}NO_2.HCl.\frac{1}{4}H_2O$: Calculated: C, 65.87; H, 9.48; N, 4.04. Found: C, 65.79; H, 9.08; N, 3.95.

EXAMPLE 32

1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohex-2-en-1-ol

By replacing 4-bromo-N,N-dimethylbenzeneacetamide with a molar equivalent of 4-methoxy-N,N-dimethylbenzeneacetamide in Example 14, and cyclohexanone with 2-cyclohexen-1-one, was obtained the corresponding cyclohexenone derivative. This intermediate was converted following the procedure described in Example 15 to the title compound as the fumarate, m.p. 128°–130° C.

Analysis for: $C_{17}H_{25}NO_2.C_4H_4O_4$: Calculated: C, 64.4; H, 7.31; N, 3.58. Found: C, 63.8; H, 7.46; N, 3.88.

EXAMPLE 33

Resolution of Racemic 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol

1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol (48.0 g., 0.173 m) dissolved in ethyl acetate (350 ml) was treated with di-p-toluoyl-d-tartaric acid (33.5 g., 0.082 m) dissolved in ethyl acetate (250 ml). After standing overnight, the solid was filtered. The solid was recrystallized three times by dissolving in boiling ethyl acetate (300 ml) and methanol (50 ml), concentrating by boiling to incipient crystallization and chilling. Yield 31.7 g., m.p. 126°–128° C. $[\alpha]_D^{25} = -50.51$; c=1.03 ethanol.

The salt was converted to its free base by shaking in 2N sodium hydroxide and diethyl ether. The ether layer was washed with brine, dried over anhydrous sodium carbonate, evaporated and dried in vacuo. yield 16.4 g., 68.5%. m.p. 104°–5° C. $[\alpha]_D^{25} = +27.95$; c=1.15, 95% ethanol.

The base was dissolved in ether (500 ml) and treated with 4.5N hydrogen chloride in isopropanol (20 ml). The resulting hydrochloride salt was recrystallized from warm methanol (75 ml) by dilution with ether (400 ml) and chilling. Yield 16.6 g. m.p. 239°–241° C. $[\alpha]_D^{25} = -4.38$; c=1.01, 95% ethanol.

The filtrate and washings from the original di-p-toluoyl-d-tartrate salt were evaporated to dryness. The free base was obtained by shaking the solid with 2N sodium hydroxide (400 ml), extracting with diethyl ether

(3×250 ml), washing the extracts with brine and drying. Yield 24.2 g. The base was dissolved in ethyl acetate (150 ml) and treated with di-p-toluoyl-1-tartaric acid (16.75 g, 0.0435 m) dissolved in ethyl acetate (150 ml). After standing overnight the salt was filtered and was recrystallized twice from ethyl acetate (300 ml) and methanol (50 ml) as described. Yield 29.4 g. m.p. 124°-127° C. $[\alpha]_D^{25}=+50.77$, c=0.845 ethanol.

The base was obtained in the manner described. Yield 14.7 g. m.p. 104°-105° C. $[\alpha]_D^{25}=-26.56$, c=1.22%, 95% ethanol.

The free base was converted to the hydrochloride salt. Yield 14.5 g. m.p. 239°-241° C. $[\alpha]_D^{25}=+4.98$, c=1.01, 95% ethanol.

EXAMPLE 34

1-[1-(4-aminophenyl)-2-dimethylaminoethyl]cyclohexanol

17.0 g (0.095 moles) of p-aminophenylacetic acid, dimethylamide was dissolved in 500 ml of tetrahydrofuran, placed under a nitrogen atmosphere, and cooled to −20° C. 23.6 g (1.15 equivalents) of 1,1,4,4-tetramethyl-1,4-dichlorosilylethylene was added, followed dropwise by a solution of 42 g (2.4 equivalents) of sodium bis(trimethylsilyl)amide in 250 ml of THF. The mixture was allowed to warm to room temperature and was stirred for 18 hours.

The mixture was next cooled to −78° C. and 71.6 ml (1.2 equivalents) of 1.6N n-butyl lithium in hexane added. The reaction was stirred for 45 minutes and then 20 ml (2.0 equivalents) of cyclohexanone added. The mixture was stirred for an additional 1 hour at −78° C. and then poured into a saturated aqueous solution of ammonium chloride. The organic phase was removed and the aqueous phase was extracted with diethyl ether. The combined organic phases were dried over sodium sulfate, filtered and concentrated in vacuo to yield 20 g of crude 1-[(4-aminophenyl)(dimethylaminocarbonyl)-methyl]cyclohexanol. Column chromatography on silica gel with 1% methanol in methylene chloride gave 16 g of essentially pure white solid. A sample twice recrystallized from ethanol had m.p. 169°-170° C. and the following elemental analysis:

Analysis for: $C_{16}H_{24}O_2N_2$: Calculated: C, 69.51; H, 8.77; N, 10.14. Found: C, 69.69; H, 8.96; N, 10.26.

5.0 g (0.018 mole) of the above amide was dissolved in 300 ml of dry tetrahydrofuran and added dropwise to a mixture of 1.1 g of lithium aluminum hydride and 8.0 ml of concentrated sulfuric acid in 200 ml of tetrahydrofuran at 0° C. The mixture was stirred at 0° C. for five hours, then the excess reagent was destroyed by the dropwise addition of 4 ml of 50:50 THF-water, then 4 ml of 15% aqueous sodium hydroxide and finally 4 ml of water. The mixture was filtered and the precipitate washed several times with THF. The combined filtrates were evaporated and the residue recrystallized from isopropanol to give 3.8 g of the title compound as the free base. Treatment with excess oxalic acid in ethyl acetate gave the dioxalate, m.p. 105° C.(d).

Analysis for: $C_{20}H_{30}N_2O_9$: Calculated: C, 54.28; H, 6.84; N, 6.33. Found: C, 53.96; H, 6.83; N, 6.24.

EXAMPLE 35

1-[1-(4-nitrophenyl)-2-dimethylaminoethyl]cyclohexanol

2.0 g (7.6 mmoles) of 1-[1-(4-aminophenyl)-2-dimethylaminoethyl]cyclohexanol was dissolved in 50 ml of methylene chloride and added dropwise to a stirring solution of 2.2 g (2.5 equivalents) of nitrosonium tetrafluoroborate. The reaction was stirred at room temperature for four hours. The methylene chloride was then removed in vacuo and replaced with 100 ml of water. This solution was added slowly to a mixture of 2.0 g of copper in 200 ml of 1N sodium nitrite and the combination stirred for 2 hours at room temperature. Extraction with methylene chloride, drying, and evaporation in vacuo yielded 2.0 g of the free base of the title compound. Recrystallization from isopropanolic HCl gave the hydrochloride, m.p. 211°-212° C.

Analysis for: $C_{16}H_{24}O_3N_2$: Calculated: C, 58.42; H, 7.37; N, 8.52. Found: C, 58.03; H, 7.53; N, 8.69.

EXAMPLE 36

1-[2-dimethylamino)-1-(3-bromo-4-methoxyphenyl)ethyl]cyclohexanol

By replacing 1-[2-amino-1-(p-methoxyphenyl)ethyl]-cyclohexanol in Example 3 with a molar equivalent amount of 1-[2-amino-1-(3-bromo-4-methoxyphenyl)ethyl]cyclohexanol and refluxing overnight, the title compound was obtained, m.p. 218°-220° C.

Analysis for: $C_{17}H_{26}NO_2Br.HCl$: Calculated: C, 57.98; H, 6.92; N, 3.56. Found: C, 51.57; H, 6.79; N, 3.46.

EXAMPLE 37

1-[2-[1-(dimethylamino)-2-(4-methoxyphenyl)propyl]-]cyclohexanol

14.7 g (0.10 mole) of p-methoxyphenylacetonitrile was dissolved in 250 ml of dry tetrahyrofuran and placed in a dry ice/isopropanol bath under N_2. 69.0 ml of 1.6M n-butyl lithium (0.11 mole) was added dropwise over 30 minutes and the mixture stirred at −78° C. for one hour. The lithium salt of the nitrile precipitated as a yellow solid during this time. 71.0 g (0.50 mole) of methyl iodide was then added and stirring at −78° C. continued for an additional hour. The mixture was then poured into saturated ammonium chloride and the product extracted into diethyl ether, washed with saturated sodium chloride and dried over sodium sulfide. It was filtered and evaporated, redissolved in methylene chloride and passed through Florisel ®. Evaporation gave 15.0 g of α-(p-methoxyphenyl)propionitrile as an orange oil.

The α-(p-methoxyphenyl)propionitrile prepared above was redissolved in 250 ml of tetrahydrofuran and cooled to −78° C. in dry ice/isopropanol. 69.0 ml of 1.6M n-butyllithium was added over 30 minutes and the mixture stirred for 1 hour under nitrogen. 20 ml of cyclohexanone was then added and stirring at 078° C. was continued for an additional hour. The mixture was poured into saturated ammonium chloride solution and the product extracted with diethyl ether. It was washed with water, saturated sodium chloride and dried over sodium sulfate. Filtration and evaporation gave 21.5 g of white solid. A sample twice recrystallized from benzene had m.p. 129° C. and the following analysis:

Analysis for: $C_{16}H_{21}NO_2$: Calculated: C, 74.10; H, 8.16; N, 5.40. Found: C, 73.95; H, 8.04; N, 5.29.

4.0 g (15 mmoles) of the β-hydroxynitrile prepared above was dissolved in 200 ml of tetrahydrofuran and 50 ml of 1M borane tetrahydrofuran complex was added. The mixture was refluxed for 2 hours and allowed to cool. 200 ml of 2N HCl was added and the THF removed in vacuo. The aqueous solution was made basic by the addition of solid pottasium carbonate

and the product extracted with 500 ml of ethyl acetate, washed with saturated sodium chloride and dried over sodium sulfate. This was filtered and evaporated and treated with isopropanolic HCl and diethyl ether to yield 3.3 g of the primary amine, m.p. 209° C.

Analysis for: $C_{16}H_{26}NO_2Cl$: Calculated: C, 64.09; H, 8.74; N, 4.67. Found: C, 63.70; H, 8.60; N, 4.59.

3.0 g (10 mmole) of the primary amine hydrochloride was dissolved in 200 ml of absolute ethanol. 5.0 ml of 37% aqueous formaldehyde and 1.0 g of 10% palladium on carbon were added and the mixture was treated with 50 psi of hydrogen on a Parr shaker for 3 days. The mixture was then filtered and evaporated and the solvent replaced with 300 ml of water and washed with 300 ml of ethyl acetate. The aqueous solution was then made pasic with solid sodium carbonate and again extracted with ethyl acetate. The organic extract was washed with saturated brine and dried over sodium sulfate. It was filtered and evaporated and the title compound precipitated as the hydrochloride from isopropanol/ether by the addition of isopropanolic HCl. A second crystallization from isopropanol gave 2.0 g of white solid, m.p. 271° C.

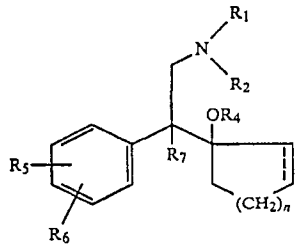
Analysis for: $C_{18}H_{30}NO_2Cl$: Calculated: C, 65.93; H, 9.22; N, 4.27. Found: C, 65.73; H, 8.93; N, 4.20.

EXAMPLE 38

By following a procedure similar to Examples 13 to 15, using (a) 3,4-dibromophenylacetic acid, (b) 3-methylphenylacetic acid, (c) 4-bromophenylacetic acid and (d) 3-methoxyphenylacetic acid instead of p-bromophenylacetic acid and, as the cycloalkanone, (a) cyclohexanone, (b) cyclohexanone, (c) cyclobutanone and (d) cyclopentanone, there are prepared (a) 1-[1-(3,4-dibromophenyl)-2-(dimethylamino)ethyl]cyclohexanol, (b) 1-[2-(dimethylamino)-1-(3-methylphenyl)ethyl]cyclohexanol, (c) 1-[1-(4-bromophenyl)-2-(dimethylamino)ethyl]cyclobutanol and (d) 1-[2-(dimethylamino)-1-(3-methoxyphenyl)ethyl]cyclopentanol.

What is claimed is:

1. A compound of the formula:



wherein

the dotted line represents optional olefinic unsaturation, and

R_1 is hydrogen or alkyl of 1 to 6 carbon atoms;

R_2 is alkyl of 1 to 6 carbon atoms;

R_4 is hydrogen, alkyl of 1 to 6 carbon atoms, formyl, or alkanoyl of 2 to 7 carbon atoms;

R_5 and R_6 are independently hydrogen, hydroxyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, nitro, alkylmercapto of 1 to 6 carbon atoms, amino, alkylamino of 1 to 6 carbon atoms, dialkylamino in which each alkyl group is of 1 to 6 carbon atoms, alkanamido of 2 to 7 carbon atoms, halo, or trifluoromethyl;

R_7 is hydrogen or alkyl of 1 to 6 carbon atoms; and

n is one of the integers 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1 in which in which R_1 is hydrogen or alkyl of 1 to 3 carbon atoms; R_2 is alkyl of 1 to 3 carbon atoms; R_5 is hydrogen, alkoxy of 1 to 3 carbon atoms, chloro, bromo, trifluoromethyl or alkyl of 1 to 3 carbon atoms; R_6 is alkyl of 1 to 3 carbon atoms, alkoxy of 1 to 3 carbon atoms, chloro, bromo, trifluoromethyl or alkanoyloxy of 2 to 3 carbon atoms; R_7 is hydrogen or alkyl of 1 to 3 carbon atoms; or a pharmaceutically acceptable salt thereof.

3. A compound of claim 2 in which R_5 and R_6 are in meta or para positions and n is 2.

4. The compound of claim 1 which is 1-[(2-dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

5. The compound of claim 1 which is 1-(α-[(dimethylamino)methyl]benzyl)cyclohexanol or a pharmaceutically acceptable salt thereof.

6. The compound of claim 1 which is 1-(α-[methylamino)methyl]benzyl)cyclohexanol or a pharmaceutically acceptable salt thereof.

7. The compound of claim 1 which is 1-[1-(4-chlorophenyl)-2-(dimethylamino)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

8. The compound of claim 1 which is 1-[1-(4-methoxyphenyl)-2-(methylamino)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

9. The compound of claim 1 which is 1-[1-(4-bromophenyl-2-(dimethylamino)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

10. The compound of claim 1 which is 1-[1-(3-bromophenyl)-2-(dimethylamino)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

11. The compound of claim 1 which is 1-[1-(3-chlorophenyl)-2-(dimethylamino)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

12. The compound of claim 1 which is 1-[1-(2-chlorophenyl)-2-(dimethylamino)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

13. The compound of claim 1 which is 1-[1-(3,4-dichlorophenyl)-2-(dimethylamino)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

14. The compound of claim 1 which is 1-[2-[1-(dimethylamino)-2-(4-methoxyphenyl)propyl]]cyclohexanol or a pharmaceutically acceptable salt thereof.

15. The compound of claim 1 which is 1-[2-(dimethylamino)-1-(3-methoxyphenyl)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

16. The compound of claim 1 which is 1-[1-(3,4-dimethoxyphenyl)-2-(dimethylamino)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

17. The compound of claim 1 which is 1-[2-(dimethylamino)-1-(4-trifluoromethylphenyl)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

18. The compound of claim 1 which is 1-[2-(dimethylamino)-1-(3-trifluoromethylphenyl)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

19. The compound of claim 1 which is 1-[2-(dimethylamino)-1-(4-methylphenyl)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

20. The compound of claim 1 which is 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohex-2-en-1-ol or a pharmaceutically acceptable salt thereof.

21. The compound of claim 1 which is 1-[2-(dimethylamino)-1-(4-hydroxyphenyl)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

22. The compound of claim 1 which is 1-[2-(dimethylamino)-1-(3-hydroxyphenyl)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

23. The compound of claim 1 which is 1-[1-(4-aminophenyl)-2-(dimethylamino)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

24. The compound of claim 1 which is 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclopentanol or a pharmaceutically acceptable salt thereof.

25. The compound of claim 1 which is 1-[1-(4-nitrophenyl)-2-(dimethylamino)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

26. The compound of claim 1 which is 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cycloheptanol or a pharmaceutically acceptable salt thereof.

27. The compound of claim 1 which is 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclooctanol or a pharmaceutically acceptable salt thereof.

28. The compound of claim 1 which is 1-[2-(dimethylamino)-1-(3-bromo-4-methoxyphenyl)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

29. The compound of claim 1 which is 1-[1-(3,4-dibromophenyl)-2-(dimethylamino)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

30. The compound of claim 1 which is 1-[(2-dimethylamino)-1-(3-methylphenyl)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

31. The compound of claim 1 which is 1-[1-(4-bromophenyl-2-(dimethylamino)ethyl]cyclobutanol or a pharmaceutically acceptable salt thereof.

32. The compound of claim 1 which is 1-[2-(dimethylamino)-1-(3-methoxyphenyl)ethyl]cyclopentanol or a pharmaceutically acceptable salt thereof.

* * * * *

EXHIBIT E

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE EXTENDING PATENT TERM UNDER 35 U.S.C. § 156

PATENT NO. : 4,535,186

DATED : August 13, 1985

INVENTOR(S) : G. E. Morris Husbands et al.

PATENT OWNER : American Home Products

This is to certify that there has been presented to the

COMMISSIONER OF PATENTS AND TRADEMARKS

an application under 35 U.S.C. § 156 for an extension of the patent term. Since it appears that the requirements of the law have been met, this certificate extends the term of the patent for the period of

FIVE YEARS

from the original expiration date of the patent, December 13, 2002, subject to the requirements of 35 U.S.C. § 41, with all rights pertaining thereto as provided by 35 U.S.C. § 156(b).

I have caused the seal of the Patent and Trademark Office to be affixed this 25th day of April 1996.

Bruce A. Lehman

Assistant Secretary of Commerce and
Commissioner of Patents and Trademarks

EXHIBIT F

ENTIRE EXHIBIT REDACTED

EXHIBIT G

EXTENDED RELEASE FORMULATION

This application claims priority to Provisional Application No. 60/014,016 filed March 25, 1996.

Background of the invention

Extended release drug formulations are conventionally produced as compressed tablets by hydrogel tablet technology. To produce these sustained release tablet drug dosage forms, the active ingredient is conventionally compounded with cellulose ethers such as methyl cellulose, ethyl cellulose or hydroxypropylmethylcellulose with or without other excipients and the resulting mixture is pressed into tablets. When the tablets are orally administered, the cellulose ethers in the tablets swell upon hydration from moisture in the digestive system, thereby limiting exposure of the active ingredient to moisture. As the cellulose ethers are gradually leached away by moisture, water more deeply penetrates the gel matrix and the active ingredient slowly dissolves and diffuses through the gel, making it available for absorption by the body. An example of such a sustained release dosage form of the analgesic/antiinflammatory drug etodolac (Lodine®) appears in US patent 4,966,768. US patent 4,389,393 discloses sustained release therapeutic compressed solid unit dose forms of an active ingredient plus a carrier base comprised of a high molecular weight hydroxypropylmethylcellulose, methyl cellulose, sodium carboxymethylcellulose and or other cellulose ether.

Where the production of tablets is not feasible, it is conventional in the drug industry to prepare encapsulated drug formulations which provide extended or sustained release properties. In this situation, the extended release capsule dosage forms may be formulated by mixing the drug with one or more binding agents to form a uniform mixture which is then moistened with water or a solvent such as ethanol to form an extrudable plastic mass from which small diameter, typically 1 mm, cylinders of drug/matrix are extruded, chopped into appropriate lengths and transformed into spheroids using standard spheronization equipment. The spheroids, after drying, may then be film-coated to retard dissolution. Gelatin capsules are filled with the film-coated spheroids in the quantity needed to obtain the desired therapeutic effect. Spheroids releasing the drug at different rates may be combined in a gelatin capsule to obtain desired release rates and blood levels. US patent 4,138,475 discloses a sustained release pharmaceutical composition consisting of a hard gelatin capsule filled with film-coated spheroids comprised of propanolol in admixture with microcrystalline cellulose wherein the film coating is composed of ethyl cellulose, optionally with hydroxypropylmethylcellulose and/or a plasticizer.

Venlafaxine, 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol, is an important drug in the neuropharmacological arsenal used for treatment of depression. Venlafaxine and the acid addition salts thereof are disclosed in US patent 4,535,186. Venlafaxine hydrochloride is presently administered to adults in compressed tablet form in doses ranging from 75 to 350 mg/day , in divided doses two or three times a day. In therapeutic dosing with venlafaxine hydrochloride tablets, rapid dissolution results in a rapid increase in blood plasma levels of the active compound shortly after administration followed by a decrease in blood plasma levels over several hours as the active compound is eliminated or metabolized, until sub-therapeutic plasma levels are approached after about twelve hours following administration, thus requiring additional dosing with the drug. With the plural daily dosing regimen, the most common side effect is nausea, experienced by about forty five percent of patients under treatment with venlafaxine hydrochloride. Vomiting also occurs in about seventeen percent of the patients.

Brief Description of the Invention

In accordance with this invention, there is provided an extended release (ER), encapsulated formulation containing venlafaxine hydrochloride as the active drug component, which provides in a single dose, a therapeutic blood serum level over a twenty four hour period.

Through administration of the venlafaxine formulation of this invention, there is provided a method for obtaining a flattened drug plasma concentration to time profile, thereby affording a tighter plasma therapeutic range control than can be obtained with multiple daily dosing. In other words, this invention provides a method for eliminating the sharp peaks and troughs (hills and valleys) in blood plasma drug levels induced by multiple daily dosing with conventional immediate release venlafaxine hydrochloride tablets. In essence, the plasma levels of venlafaxine hydrochloride rise, after administration of the extended release formulations of this invention, for between about five to about eight hours (optimally about six hours) and then begin to fall through a protracted, substantially linear decrease from the peak plasma level for the remainder of the twenty four hour period, maintaining at least a threshold therapeutic level of the drug during the entire twenty-four period. In contrast, the conventional immediate release venlafaxine hydrochloride tablets give peak blood plasma levels in 2 to 4 hours. Hence, in accordance with the use aspect of this invention, there is provided a method for moderating the plural blood plasma peaks and valleys attending the pharmacokinetic utilization of multiple daily tablet dosing with

venlafaxine hydrochloride which comprises administering to a patient in need of treatment with venlafaxine hydrochloride, a one-a-day, extended release formulation of venlafaxine hydrochloride.

The use of the one-a-day venlafaxine hydrochloride formulations of this invention reduces by adaptation, the level of nausea and incidence of emesis that attend the administration of multiple daily dosing. In clinical trials of venlafaxine hydrochloride ER, the probability of developing nausea in the course of the trials was greatly reduced after the first week. Venlafaxine ER showed a statistically significant improvement over conventional venlafaxine hydrochloride tablets in two eight-week and one 12 week clinical studies. Thus, in accordance with this use aspect of the invention there is provided a method for reducing the level of nausea and incidence of emesis attending the administration of venlafaxine hydrochloride which comprises dosing a patient in need of treatment with venlafaxine hydrochloride with an extended release formulation of venlafaxine hydrochloride once a day in a therapeutically effective amount.

Detailed Description of the Invention

1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol hydrochloride is polymorphic. Of the forms isolated and characterized to date, Form I is considered to be the kinetic product of crystallization which can be converted to Form II upon heating in the crystallization solvent. Forms I and II cannot be distinguished by their melting points but do exhibit some differences in their infrared spectra and X-ray diffraction patterns. Any of the polymorphic forms such as Form I or Form II may be used in the formulations of the present invention.

The extended release formulations of this invention are comprised of 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride in admixture with microcrystalline cellulose and hydroxypropylmethylcellulose. Formed as beads or spheroids, the drug containing formulation is coated with a mixture of ethyl cellulose and hydroxypropylmethyl cellulose to provide the desired level of coating, generally from about two to about twelve percent on a weight/weight basis of final product or more preferably from about five to about ten percent (w/w) , with best results obtained at from about 6 to about 8 percent (w/w). More specifically, the extended release spheroid formulations of this invention comprise from about 30 to 40 percent venlafaxine hydrochloride, from about 50 to about 70 percent microcrystalline cellulose, NF, from about 0.25 to about 1 percent hydroxypropylmethylcellulose, USP, and from about 5 to about 10 percent film coating, all on a weight/weight basis. And preferably, the spheroid formulations contain about 35

percent venlafaxine hydrochloride, about 55 to 60 percent microcrystalline cellulose NF (Avicel® PH101), about one half percent hydroxypropyl methylcellulose 2208 USP (K3, Dow, which has a viscosity of 3 cps for 2% aqueous solutions, a methoxy content of 19–24% and a hydroxypropoxy content of 4–13%), and from about 6 to 8 percent film coating.

The film coating is comprised of 80 to 90 percent of ethyl cellulose, NF and 10 to 20 percent hydroxypropyl methylcellulose (2910), USP on a weight/weight basis. Preferably the ethyl cellulose has a ethoxy content of 44.0–51% and a viscosity of 50 cps for a 5% aqueous solution and the hydroxypropylmethylcellulose is USP 2910 having a viscosity of 6 cps at 2% aqueous solution with a methoxy content of 28–30% and a hydroxypropoxy content of 7–12%. The ethyl cellulose used herein is Aqualon HG 2834.

Other equivalents of the hydroxypropylmethylcelluloses 2208 and 2910 USP and ethyl cellulose, NF, having the same chemical and physical characteristics as the proprietary products named above may be substituted in the formulation without changing the inventive concept.

It was completely unexpected that an extended release formulation containing venlafaxine hydrochloride could be obtained because the hydrochloride of venlafaxine proved to be extremely water soluble. Numerous attempts to produce extended release tablets by hydrogel technology proved to be fruitless because the compressed tablets were either physically unstable (poor compressibility or capping problems) or dissolved too rapidly in dissolution studies. Typically, the tablets prepared as hydrogel sustained release formulations gave 40-50% dissolution at 2 hrs, 60-70% dissolution at 4 hrs and 85-100% dissolution at 8 hrs.

Numerous spheroid formulations were prepared using different grades of microcrystalline cellulose and hydroxypropyl methylcellulose, different ratios of venlafaxine hydrochloride and filler, different binders such as polyvinylpyrrolidone, methylcellulose, water, and polyethylene glycol of different molecular weight ranges in order to find a formulation which would provide a suitable granulation mix which could be extruded properly. In the extrusion process, heat buildup occurred which dried out the extrudate so much that it was difficult to convert the extruded cylinders into spheroids. Addition of hydroxypropylmethylcellulose 2208 to the venlafaxine hydrochloride–microcrystalline cellulose mix made production of spheroids practical.

The following examples are presented to illustrate applicant's solution to the problem of preparation of the extended release drug containing formulations of this invention.

Example 1.

VENLAFAXINE HYDROCHLORIDE EXTENDED RELEASE CAPSULES

A mixture of 44.8 parts (88.4 % free base) of venlafaxine hydrochloride, 74.6 parts of the microcrystalline cellulose, NF, and 0.60 parts of hydroxypropylmethyl cellulose 2208, USP, are blended with the addition of 41.0 parts water. The plastic mass of material is extruded, spheronized and dried to provide uncoated drug containing spheroids.

Stir 38.25 parts of ethyl cellulose, NF, HG2834 and 6.75 parts of hydroxypropyl methylcellulose 2910, USP in a 1:1 v/v mixture of methylene chloride and anhydrous methanol until solution of the film coating material is complete.

To a fluidized bed of the uncoated spheroids is applied 0.667 parts of coating solution per part of uncoated spheroids to obtain extended release, film coated spheroids having a coating level of 3%.

The spheroids are sieved to retain the coated spheroids of a particle size between 0.85 mm to 1.76 mm diameter. These selected film coated spheroids are filled into hard gelatin capsules conventionally.

Example 2.

Same as for Example 1 except that 1.11 parts of the film coating solution per part of uncoated spheroids is applied to obtain a coating level of 5%.

Example 3.

Same as for Example 1 except that 1.33 parts of the film coating solution is applied to 1 part of uncoated spheroids to obtain a coating level of 6%.

Example 4.

Same as for Example 1 except that 1.55 parts of the film coating solution is applied to 1 part of uncoated spheroids to obtain a coating level of 7%.

The test for acceptability of the coating level is determined by analysis of the dissolution rate of the finished coated spheroids prior the encapsulation. The dissolution procedure followed uses USP Apparatus 1 (basket) at 100 rpm in purified water at 37°C. Conformance with the dissolution rate given in Table 1 provides the twenty-four hour therapeutic blood levels for the drug component of the extended release capsules of this invention in capsule form. Where a given batch of coated spheroids releases drug too slowly to comply with the desired dissolution rate study, a portion of uncoated spheroids

or spheroids with a lower coating level may be added to the batch to provide, after thorough mixing, a loading dose for rapid increase of blood drug levels. A batch of coated spheroids that releases the drug too rapidly can receive additional film-coating to give the desired dissolution profile.

Table 1

Acceptable Coated Spheroid Dissolution Rates

Time (hours)	Average % Venlafaxine HCL released
2	<30
4	30-55
8	55-80
12	65-90
24	>80

Batches of the coated venlafaxine hydrochloride containing spheroids which have a dissolution rate corresponding to that of Table 1 are filled into hard gelatin capsules in an amount needed to provide the unit dosage level desired. The standard unit dosage immediate release (IR) tablet used presently provides amounts of venlafaxine hydrochloride equivalent to 25 mg, 37.5 mg, 50 mg, 75 mg and 100 mg venlafaxine. The capsules of this invention are filled to provide an amount of venlafaxine hydrochloride equivalent to that presently used in tablet form and also up to about 150 mg venlafaxine hydrochloride.

Dissolution of the venlafaxine hydrochloride ER capsules is determined as directed in the U. S. Pharmacopoeia (USP) using apparatus 1 at 100 rpm on 0.9 L of water. A filtered sample of the dissolution medium is taken at the times specified. The absorbance of the clear solution is determined from 240 to 450 nanometers (nm) against the dissolution medium. A baseline is drawn from 450 nm through 400 nm and extended to 240 nm. The absorbance at the wavelength of maximum absorbance (about 274 nm) is determined with respect to this baseline. Six hard gelatin capsules are filled with the theoretical amount of venlafaxine hydrochloride spheroids and measured for dissolution. Standard samples consist of venlafaxine hydrochloride standard solutions plus a gelatin capsule correction solution. The percentage of venlafaxine released is determined from the equation

$$\% \text{ Venlafaxine hydrochloride released} = \frac{(As)(Wr)(S)(V1)(0.888)(100)}{(Ar)(V2)(C)}$$

where As is absorbance of sample preparation, Wr is weight of reference standard, mg; S is strength of the reference standard, decimal; V1 is the volume of dissolution medium used to dissolve the dosage form, mL; 0.884 is the percent free base, Ar is the absorbance of the standard preparation, V2 is the volume of reference standard solution, mL; and C is the capsule claim in mg.

Table 2 shows the plasma level of venlafaxine versus time for one 75 mg conventional Immediate Release (IR) tablet administered every 12 hours, two 75 mg extended release (ER) capsules administered simultaneously every 24 hours, and one 150 mg extended release (ER) capsule administered once every 24 hours in human male subjects. The subjects were already receiving venlafaxine hydrochloride according to the dosage protocol, thus the plasma blood level at zero time when dosages were administered is not zero.

Table 2

Plasma venlafaxine level (ng/mL) versus time, conventional tablet (not extended release) versus ER capsule

Time (hours)	75 mg (IR)tablet (q 12 h)	2 x 75 mg (ER)capsules (q 24 hr)	1 x 150 mg (ER)capsules (q 24 h)
0	62.3	55.0	55.8
0.5	76.3		
1	135.6	53.3	53.2
2	212.1	69.8	70.9
4	162.0	138.6	133.3
6	114.6	149.0	143.5
8	86.7	129.3	129.5
10		118.4	114.4
12	51.9	105.1	105.8
12.5	74.7		
13	127.5		
14	161.3	90.5	91.3
16	134.6	78.2	78.5
18	106.2		
20	83.6	62.7	63.3
24	57.6	56.0	57.3

Table 2 shows that the plasma levels of two 75 mg/capsule venlafaxine hydrochloride ER capsules and one 150 mg/capsule venlafaxine hydrochloride ER capsule provide very similar blood levels. The data also show that the plasma level after 24 hours for either extended release regimen is very similar to that provided by two immediate release 75 mg tablets of venlafaxine hydrochloride administered at 12 hour intervals.

Further, the plasma levels of venlafaxine obtained with the extended release formulation do not increase to the peak levels obtained with the conventional immediate release tablets given 12 hours apart. The peak level of venlafaxine from (ER), somewhat

below 150 ng/ml, is reached in about six hours, plus or minus two hours, based upon this specific dose when administered to patients presently under treatment with venlafaxine hydrochloride (IR). The peak plasma level of venlafaxine, somewhat over 200 ng/ml, following administration of (IR) is reached in two hours and falls rapidly thereafter.

Table 3 shows venlafaxine blood plasma levels in male human subjects having a zero initial blood plasma level. Again, a peak blood plasma concentration of venlafaxine is seen at about 6 hours after dosing with venlafaxine hydrochloride extended release capsules in the quantities indicated. The subjects receiving the single 50 mg immediate release tablet showed a peak plasma level occurring at about 4 hours. For comparative purposes, the plasma levels of venlafaxine for subjects receiving the conventional formulated tablet can be multiplied by a factor of three to approximate the plasma levels expected for a single dose of 150 mg. conventional formulation.

Table 3. Plasma Blood Levels in Human Males Having No Prior Venlafaxine Blood Level

Time (Hours)	1 x 50 mg IR tablet	2 x 75 mg ER capsules	1 x 150 mg ER capsule
0	0	0	0
1	27.87	1.3	0
1.5	44.12	6.0	2.2
2	54.83	20.6	12.8
4	66.38	77.0	81.0
6	49.36	96.5	94.4
8	30.06	93.3	86.9
10	21.84	73.2	72.8
12	15.91	61.3	61.4
14	13.73	52.9	51.9
16	10.67	47.5	41.1
20	5.52	35.2	34.0
24	3.56	29.3	28.5
28	2.53	23.4	22.9
36	1.44	11.9	13.5
48	0.66	5.8	5.2

The blood plasma levels of venlafaxine were measured according to the following procedure. Blood samples from the subjects were collected in heparinized evacuated blood tubes and the tubes were inverted gently several times. As quickly as possible, the tubes were centrifuged at 2500 rpm for 15 minutes. The plasma was pipetted into plastic tubes and stored at -20°C until analysis could be completed.

To 1 mL of each plasma sample in a plastic tube was added 150 µL of a stock internal standard solution (150 µg/ml). Saturated sodium borate (0.2 mL) solution was added to each tube and vortexed. Five mL of ethyl ether was added to each tube which were then capped and shaken for 10 minutes at high speed. The tubes were centrifuged at 3000 rpm for 5 minutes. The aqueous layer was frozen in dry ice and the organic layer transferred to a clean screw cap tube. A 0.3 mL portion of 0.01 N HCl solution was added to each tube and shaken for 10 minutes at high speed. The aqueous layer was frozen and the organic layer removed and discarded. A 50µL portion of the mobile phase (23:77 acetonitrile:0.1M monobasic ammonium phosphate buffer, pH 4.4) was added to each tube, vortexed, and 50 µL samples were injected on a Supelco Supelcoil LC-8-DB, 5 cm x 4.6 mm, 5 µ column in a high pressure liquid chromatography apparatus equipped with a Waters Lambda Max 481 detector or equivalent at 229 nm. Solutions of venlafaxine hydrochloride at various concentrations were used as standards.

Thus, the desired dissolution rate of a sustained release dosage form of venlafaxine hydrochloride, impossible to achieve with hydrogel tablet technology, has been achieved with the film-coated spheroid compositons of this invention.

What is claimed is:

1. An encapsulated, extended release formulation of venlafaxine hydrochloride comprising a hard gelatin capsule containing a therapeutically effective amount of spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and hydroxypropyl methylcellulose coated with ethyl cellulose and hydroxypropylmethylcellulose.

2. An extended release formulation according to claim 1 wherein the spheroids are composed of about 37.3% by weight of venlafaxine hydrochloride, about 0.5% by weight of hydroxypropylmethylcellulose 2208, and about 62.17% by weight of microcrystalline cellulose.

3. A composition according to claim 1 wherein the film coating is comprised of ethyl cellulose (4.81% of total weight) and hydroxypropylmethylcellulose (0.85% of total weight).

4. A composition according to claim 1 wherein the film coating is comprised of ethyl cellulose (4.04% of total weight) and hydroxypropylmethylcellulose (0.714% of total weight).

5. A composition according to claim 1 wherein the film coating is comprised of ethyl cellulose (2.48% of total weight) and hydroxypropylmethylcellulose (0.437% of total weight).

6 A film coating composition which is composed of ethyl cellulose (15% of total weight), having a 44.0-51.0% content of ethoxy groups, and hydroxypropylmethylcellulose (85% of total weight) having a methoxy content of 28.0-30.0% and a hydroxypropoxy group content of 7.0-12.0%.

7. An extended release formulation of venlafaxine hydrochloride for once daily administration which comprises spheroids containing 37.3% venlafaxine, 62.17% microcrystalline cellulose and 0.5% hydroxypropylmethylcellulose type 2208, coated with a quantity of a mixture comprised of 15% ethyl cellulose type HG 2834 and 85% hydroxypropyl-methylcellulose type 2910 sufficient to give coated spheroids having a dissolution profile which gives the desired release rate over a 24 hour period.

8. An extended release formulation of venlafaxine hydrochloride according to claim 7 which provides lower peak serum levels of up to 150 ng/ml and extended therapeutically effective plasma levels over a twenty four hour period.

9. A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty four hour period with diminished incidences of nausea and emesis which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation of claim 1 which provides a peak blood plasma level of venlafaxine in from about four to about eight hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

10. A method for eliminating the troughs and peaks of drug concentration in a patients blood plasma attending the therapeutic metabolism of plural daily doses of which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation of claim 1 which provides a peak blood plasma level of venlafaxine in from about four to about eight hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

08/821,13

ABSTRACT

EXTENDED RELEASE FORMULATION

This invention relates to a 24 hour extended release dosage formulation and unit dosage form thereof of venlafaxine hydrochloride, an antidepressant, which provides better control of blood plasma levels than conventional tablet formulations which must be administered two or more times a day and further provides a lower incidence of nausea and vomiting than the conventional tablets.

EXHIBIT H

UNITED S[illegible]ES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/821,137	03/20/97	SHERMAN D	AHP-95011

15M2/0805
RONALD W. ALICE
AMERICAN HOME PRODUCTS CORPORATION
ONE CAMPUS DRIVE
PARSIPPANY NJ 07054

EXAMINER	
HULINA, A	
ART UNIT	PAPER NUMBER
1501	8

DATE MAILED: 08/05/97

INTERVIEW SUMMARY

All participants (applicant, applicant's representative, PTO personnel):

(1) Amy Hulina (3) _____

(2) Robert Boswell, Jr. (4) _____

Date of Interview 7/30/97

Type: ☒ Telephonic ☐ Personal (copy is given to ☐ applicant ☐ applicant's representative).

Exhibit shown or demonstration conducted: ☐ Yes ☒ No If yes, brief description: _____

Agreement ☒ was reached. ☐ was not reached.

Claim(s) discussed: 6, 9 and 10

Identification of prior art discussed: Upton et al. (5,506,270)

Description of the general nature of what was agreed to if an agreement was reached, or any other comments: Agreed to amend claims 9 and 10 to depend from claim 1 to avoid rejection over Upton which discloses extended release venlafaxine at col. 3, lines 25-27.

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendments which would render the claims allowable is available, a summary thereof must be attached.)

1. ☐ It is not necessary for applicant to provide a separate record of the substance of the interview.

Unless the paragraph above has been checked to indicate to the contrary, A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a response to the last Office action has are ready been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW.

2. ☐ Since the Examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action. Applicant is not relieved from providing a separate record of the interview unless box 1 above is also checked.

Examiner Note: You must sign this form unless it is an attachment to another form.

FORM PTOL-413 (REV.1-96)

EXHIBIT I

US005506270A

United States Patent [19]

Upton et al.

[11] Patent Number: 5,506,270

[45] Date of Patent: Apr. 9, 1996

[54] **VENLAFAXINE IN THE TREATMENT OF HYPOTHALAMIC AMENORRHEA IN NON-DEPRESSED WOMEN**

[75] Inventors: **Gertrude V. Upton**, Radnor; **Albert T. Derivan**, Villanova; **Richard L. Rudolph**, Berwyn, all of Pa.

[73] Assignee: **American Home Products Corporation**, Madison, N.J.

[21] Appl. No.: **380,903**

[22] Filed: **Jan. 30, 1995**

[51] **Int. Cl.**[6] **A61K 31/045**; A01N 31/00

[52] **U.S. Cl.** **514/730**; 564/157; 564/219; 564/336; 549/443; 549/444; 514/646; 514/653; 514/659; 514/727; 514/729; 514/899

[58] **Field of Search** 564/157, 219, 564/336; 549/443, 444; 514/646, 653, 659, 727, 729, 730, 899

[56] **References Cited**

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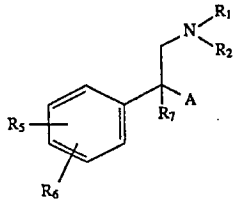
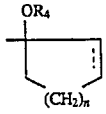
Primary Examiner—Samuel A. Acquah
Attorney, Agent, or Firm—Steven R. Eck

[57] **ABSTRACT**

This invention provides a method for treating hypothalamic amenorrhea in a non-depressed female mammal by administering to the mammal an effective amount of a hydroxycycloalkanephenethyl amine compound of the following structural formula:



in which A is a moiety of the formula



wherein

the dotted line represents optional unsaturation;

R_1 is hydrogen or alkyl;

R_2 is alkyl;

R_4 is hydrogen, alkyl, formyl, or alkanol;

R_5 and R_6 are, independently, hydrogen, hydroxyl, alkyl, alkoxy, alkanoyloxy, cyano, nitro, alkylmercapto, amino, alkylamino, dialkylamino, alkanamido, halo, trifluoromethyl, or taken together, methylene dioxy;

R_7 is hydrogen or alkyl; and

n is 0, 1, 2, 3, or 4;
or a pharmaceutically acceptable salt thereof.

13 Claims, No Drawings

VENLAFAXINE IN THE TREATMENT OF HYPOTHALAMIC AMENORRHEA IN NON-DEPRESSED WOMEN

This invention comprises a new use for venlafaxine. More particularly, this invention comprises a method for treating hypothalamic amenorrhea (HA) in a non-depressed female mammal, preferably in a non-depressed human female.

BACKGROUND OF THE INVENTION

The active ingredients of this invention, (1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol), its analogues or therapeutically acceptable salts thereof, are known generally as venlafaxine. These ingredients are disclosed in U.S. Pat. No. 4,535,186 (Husbands et al.) and have been previously reported to be useful as an antidepressant. U.S. Pat. No. 4,535,186 teaches the production of venlafaxine and its analogues and is incorporated herein by reference.

Venlafaxine has been shown to be a potent inhibitor of monoamine neurotransmitter uptake, a mechanism associated not only with demonstrated clinical antidepressant activity, but also with reproductive function by affecting indirectly the hypothalamic-pituitary-ovarian axis. Due to its novel structure, venlafaxine has a mechanism of action different from other available antidepressants, such as the tricyclic antidepressants desipramine, nortriptyline, protriptyline, imipramine, amitryptyline, trimipramine, and doxepin and different from the serotonin reuptake inhibitors (SRIs), e.g. fluoxetine, sertraline and paroxetine.

It is believed that venlafaxine's mechanism of action is related to potent inhibition of the uptake of the monoamine neurotransmitters serotonin and norepinephrine. To a lesser degree, venlafaxine also inhibits dopamine reuptake, but it has no inhibitory activity on monoamine oxidase. O-desmethylvenlafaxine, venlafaxine's major metabolite in humans, exhibits a similar pharmacologic profile. However, venlafaxine's ability to inhibit norepinephrine and serotonin (5-HT) uptake has been predicted to have an effect not just on depression but also on reproductive function through its neurotransmitter effects on the hypothalamic-pituitary-ovarian (HPO) axis.

DESCRIPTION OF THE INVENTION

The hypophysiotropic area of the hypothalamus is rich in biogenic amines (e.g., norepinephrine (NE), serotonin (5-HT) and dopamine (DA)) that can affect both the central nervous system (CNS) and endocrine system. The synthesis and release of pituitary hormones are controlled by releasing and inhibitory homones that are found in this anatomical area and controlled by the neurotransmitters 5-HT, norepinephrine, and dopamine whose afferents are located in the hypophysiotropic area and originate in the hypothalamus and in higher centers.

Altered levels of central neurotransmitters can result in a dysfunctional CNS and, in some cases, with consequent profound effects on the hypothalamic pituitary axis (HPO) resulting in impaired reproductive function.

An excess of central biogenic amines can result in altered pulse frequency and irregular amplitude of gonadotropin releasing hormone (GnRH) secretion. These changes lead to disruption of GnRH cyclicity and pituitary down-regulation by desensitization of pituitary receptors resulting in impaired secretion of luteinizing hormone (LH) and follicle stimulating hormone (FSH) and consequent impaired gonadal function. On the other hand, a deficiency of central biogenic amines decreases the synthesis and release of GnRH, but cyclicity may be normal. The effects on the pituitary are a decreased number of receptors leading to impaired secretion of LH and FSH and consequent impaired gonadal function. Thus, either excess or deficiency of neurotransmitters (namely, norepinephrine, serotonin and dopamine) may lead to impaired gonadal function.

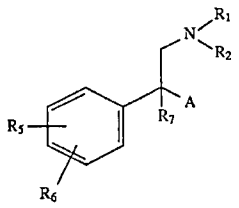
The CNS and Endocrine systems are inextricably linked and psychotropic drugs will invariably have some measurable effect on both systems. However, in the case of hypothalamic amenorrhea, one can determine the direct effect on the hypothalamic hormones by measuring gonadotropin-releasing hormone (GnRH), LH, itself, as well as the more objective endpoint of return of menses. These measures distinguish quite clearly an effective physical endpoint distinct from depression endpoints rendering depression scoring systems irrelevant. This proposed treatment is designed to cure an endocrinopathy with or without accompanying comorbidity (depression). The aim or goal of the therapy is the return of normal reproductive function.

Present therapy for hypothalamic amenorrhea uses GnRH delivered I.V. in pulsatile fashion as well as using other invasive supportive therapy, e.g. injections of human chorionic gonadotropin (HCG). The present invention delivers oral doses without the need for supportive ancillary therapy or the use of invasive techniques.

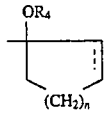
Hypothalamic amenorrhea, also known as secondary amenorrhea is the pathological absence of menstruation due to abnormal centrally mediated neuroendocrine responses affecting the hypothalamic-pituitary-ovarian axis. This cessation of menses may result following a number of occurrences, including severe stress, emotional disturbances or continuous strenuous exercise as in runners or ballet dancers, or sudden loss of body mass (anorexia nervosa), etc. unrelated to depression.

Hypothalamic amenorrhea occurs in about 5% of all menstruating women, with age distribution ranges from approximately 18 years (15%) to 41+ years (21%), reaching a maximum of 52% between ages 22 and 29. It is characterized by low to normal gonadotropins and failure to demonstrate withdrawal bleeding. It is not characterized by depression. Stressful events are known to precipitate amenorrhea and the symptoms can last from a few months to years. Infertility is the usual sequelae following loss of ovulation and menses. This disorder is usually diagnosed by an exclusionary process with particular attention to the existence of pituitary tumors. Patients suffering from hypothalamic amenorrhea have low to normal gonadotropins and some stressful event has often occurred prior to onset of the disorder. The resultant sequelae, i.e., anovulation and amenorrhea, can usually be traced to abnormal Gonadotropin Releasing Hormone (GnRH) rhythms and the restoration of normal rhythm and cyclicity, such as by the practice of the present invention, leads to a resumption of menses, ovulation and hence fertility. The method of the present invention is particularly of interest for the treatment of hypothalamic amenorrhea in non-depressed women who are otherwise physically and mentally normal.

The present invention provides a method for treating hypothalamic amenorrhea in a non-depressed mammal, preferably in a non-depressed human female. This method involves administering to the mammal one or more compounds from a group of substituted phenethylamines following the structural formula:



in which A is a moiety of the formula



wherein

the dotted line represents optional unsaturation;

R_1 is hydrogen or alkyl of 1 to 6 carbon atoms;

R_2 is alkyl of 1 to 6 carbon atoms;

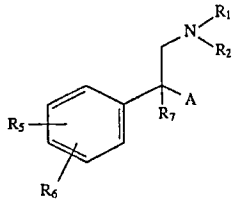
R_4 is hydrogen, alkyl of 1 to 6 carbon atoms, formyl, or alkanol of 2 to 7 carbon atoms;

R_5 and R_6 are independently hydrogen, hydroxyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, cyano, nitro, alkylmercapto of 1 to 6 carbon atoms, amino, alkylamino of 1 to 6 carbon atoms, dialkylamino in which each alkyl group is of 1 to 6 carbon atoms, alkanamido of 2 to 7 carbon atoms, halo, trifluoromethyl, or when taken together, methylene dioxy;

R_7 is hydrogen or alkyl of 1 to 6 carbon atoms; and n is one of the integers 0, 1, 2, 3, or 4;

or a pharmaceutically acceptable salt thereof.

The preferred compounds are those of the formula:



in which

A is as defined supra;

R_1 is hydrogen or alkyl of 1 to 3 carbon atoms;

R_2 is alkyl of 1 to 3 carbon atoms;

R_3 is hydrogen, hydroxy, alkoxy of 1 to 3 carbon atoms, chloro, bromo, trifluoromethyl or alkyl of 1 to 3 carbon atoms;

R_5 is hydrogen, hydroxyl, alkoxy of 1 to 3 carbon atoms, chloro, bromo, trifluoromethyl or alkyl of 1 to 3 carbon atoms;

R_6 is alkyl of 1 to 3 carbon atoms, alkoxy of 1 to 3 carbon atoms, chloro, bromo, trifluoromethyl or alkanoyloxy of 2 to 3 carbon atoms;

R_7 is hydrogen or alkyl of 1 to 3 carbon atoms;

or a pharmaceutically acceptable salt thereof.

The most preferred compounds are those in which both R_5 and R_6 are in meta positions, or one of R_5 and R_6 is in the para position, and n is 2.

Of particular interest are the compounds 1-[(2-dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol and 1-[(2-dimethylamino)-1-(4-hydoxyphenyl)ethyl]cyclohexanol and pharmaceutically acceptable salts thereof.

The compounds in which R_4 is formyl or alkanoyl of 2 to 7 carbon atoms have been found to be not as potent as the corresponding free hydroxy bearing derivatives. However, in long term therapy the acyloxy derivatives will act as pro drugs as the acyl group is removed in vivo either via acid hydrolysis in the stomach or enzymatically.

For the purposes of this disclosure and the claims that follow, it is understood that the use of venlafaxine in treating hypothalamic amenorrhea includes the use of venlafaxine's free base, its pharmaceutically acceptable salts, its racemate and its individual enantiomers, and venlafaxine analogs, both as racemates and as their individual enantiomers.

The pharmaceutically acceptable acid addition salts of the basic compounds of this invention are formed conventionally by reaction of the free base with an equivalent amount of any acid which forms a non-toxic salt. Illustrative acids are either inorganic or organic, including hydrochloric, hydrobromic, fumaric, maleic, succinic, sulfuric, phosphoric, tartaric, acetic, citric, oxalic, and similar acids. For parenteral administration, the use of water soluble salts is preferred, although either the free base of the pharmaceutically acceptable salts are applicable for oral or parenteral administration of the hypothalamic amenorrhea treating agents of this invention. The halo substituent representing R_5 or R_6 is intended to include the chloro, bromo, iodo, or fluoro substituents.

Pharmaceutical compositions containing the compounds of this invention represent an additional aspect of this invention. The active ingredient can be compounded into any of the usual oral dosage forms including tablets, capsules and liquid preparations such as elixirs and suspensions containing various coloring, flavoring, stabilizing and flavor masking substances. For compounding oral dosage forms, the active ingredient can be mixed with various conventional tabletting materials such as starch, calcium carbonate, lactose, sucrose and dicalcium phosphate to aid the tabletting or capsulating process. Magnesium stearate, as an additive, provides a useful lubricant function when desired.

The active ingredients can be dissolved or suspended in a pharmaceutically acceptable sterile liquid carrier, such as sterile water, sterile organic solvent or a mixture of both. Preferably a liquid carrier is one suitable for parenteral injection. Where the active ingredient is sufficiently soluble it can be dissolved in normal saline as a carrier; if it is too insoluble for this it can often be dissolved in a suitable organic solvent, for instance aqueous propylene glycol or polyethylene glycol solutions. Aqueous propylene glycol containing from 10 to 75% of the glycol by weight is generally suitable. In other instances other compositions can be made by dispersing the finely-divided active ingredient in aqueous starch or sodium carboxymethyl cellulose solution, or in a suitable oil, for instance arachis oil. Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by intramuscular, intraperitoneal or subcutaneous injection.

Preferably the pharmaceutical composition is in unit dosage form, e.g. as tablets or capsules. In such form, the composition is sub-divided in unit doses containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example, packeted powders or vials or ampoules. The unit dosage form can be a capsule, cachet or tablet itself, or it can be the appropriate number of any of these in package form. The quantity of the active ingredient in a unit dose of composition may be varied or adjusted from about 1 mg. or less to about 25 mg. or more, according to the particular need and the activity of the active ingredient. The usual oral recommended dose of venlafaxine

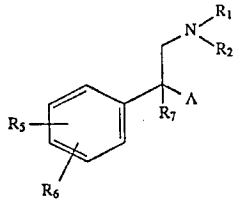
for humans may be between about 25 and about 200 mg/day or higher, not to exceed about 375 mg/day, and this dose may be administered in divided doses, preferably with food if administered orally. A maximum recommended daily dose for humans would be about 225 mg. The treatment regimen may start with the lowest dosage, such as 25 mg, and the dose may be titrated upward incrementally, such as in 25 mg increments, up to the maximum recommended dosage. The incremental increases in dosage may be conducted at monthly intervals until menses is resumed at normal cyclic intervals. At the discretion of the attending physician, the compounds of this invention may also be administered at other than daily doses.

It will be understood by one skilled in the art that dosage under this invention will be determined by the particular circumstances surrounding each case, as will the route of administration (e.g. via an oral route, transdermal route, via a pharmaceutical implant, etc.). It is understood that, while it is preferable that the compounds and pharmaceutical formulations of this invention comprise an oral dosage form, such as capsules or tablets, this invention is intended to cover any means of administration to a patient of an active amount of the compounds listed above in the treatment of hypothalamic amenorrhea. Such administrations may also be provided in a bolus form, intermittent-release form, sustained oral administration form or time-release form, which may be used to spread the doseage over time, such as for once-a-day applications.

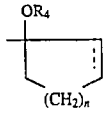
It should also be understood that the present invention is intended to include all methods of, and reasons for, treating hypothalamic amenorrhea in a non-depressed mammal, preferably in a non-depressed human, by administering to the individual an effective amount of venlafaxine or its analogues or pharmaceutically acceptable salts. For the purposes of the present invention, treating hypothalamic amenorrhea is to be understood as covering all prophylactic, therapeutic, progression inhibiting, remedial, maintenance, curative or other administrations, regimens or treatments of or with venlafaxine or its analogues or salts that yield the desired reduction of the effects of hypothalamic amenorrhea in a non-depressed mammal, preferably in a non-depressed human female.

What is claimed:

1. A method of treating hypothalamic amenorrhea in a non-depressed female mammal, the method comprising administering to the non-depressed female mammal an effective amount of a compound of the formula:



in which A is a moiety of the formula



wherein

the dotted line represents optional unsaturation;

R_1 is hydrogen or alkyl of 1 to 6 carbon atoms;

R_2 is alkyl of 1 to 6 carbon atoms;

R_4 is hydrogen, alkyl of 1 to 6 carbon atoms, formyl, or alkanol of 2 to 7 carbon atoms;

R_5 and R_6 are, independently, hydrogen, hydroxyl, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, alkanoyloxy of 2 to 7 carbon atoms, cyano, nitro, alkylmercapto of 1 to 6 carbon atoms, amino, alkylamino of 1 to 6 carbon atoms, dialkylamino in which each alkyl group is of 1 to 6 carbon atoms, alkanamido of 2 to 7 carbon atoms, halo, trifluoromethyl, or taken together, methylene dioxy;

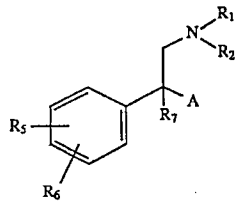
R_7 is hydrogen or alkyl of 1 to 6 carbon atoms; and

n is 0, 1, 2, 3, or 4;

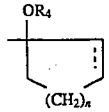
or a pharmaceutically acceptable salt thereof.

2. The method of claim 1 in which the non-depressed female mammal is a human.

3. The method of claim 1 wherein the compound of the formula:



in which A is a moiety of the formula



wherein

the dotted line represents optional unsaturation, and

R_1 is hydrogen or alkyl of 1 to 3 carbon atoms;

R_2 is alkyl of 1 to 3 carbon atoms;

R_5 is hydrogen, hydroxyl, alkoxy of 1 to 3 carbon atoms, chloro, bromo, trifuoromethyl or alkyl of 1 to 3 carbon atoms;

R_6 is alkyl of 1 to 3 carbon atoms, alkoxy of 1 to 3 carbon atoms, chloro, bromo, trifluoromethyl or alkanoyloxy of 2 to 3 carbon atoms;

R_7 is hydrogen or alkyl of 1 to 3 carbon atoms;

or a pharmaceutically acceptable salt thereof.

4. The method of claim 3 wherein R_5 and R_6 are both in meta positions, or one of R_5 and R_6 is in the para position, and n is 2.

5. The method of claim 3 wherein the compound is 1-[(2-dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

6. The method of claim 3 wherein the compound is 1-[2-(dimethylamino)-1-(4-hydroxyphenyl)ethyl]cyclohexanol or a pharmaceutically acceptable salt thereof.

7. The method of claim 3 in which the non-depressed female mammal is a human.

8. The method of claim 1 wherein the effective amount comprises a daily dose of between about 1 mg/day and about 375 mg/day.

9. The method of claim 1 wherein the effective amount comprises a daily dose of between about 25 mg/day and about 225 mg/day.

10. The method of claim 1 wherein the effective amount comprises a daily dose of between about 75 mg/day and about 200 mg/day.

11. The method of claim 3 wherein the effective amount comprises a daily dose of between about 1 mg/day and about 375 mg/day.

12. The method of claim 3 wherein the effective amount comprises a daily dose of between about 25 mg/day and about 225 mg/day.

13. The method of claim 3 wherein the effective amount comprises a daily dose of between about 75 mg/day and about 200 mg/day.

* * * * *

EXHIBIT J

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
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SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/821,137	03/20/97	SHERMAN, D	AHP-25011

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NOTICE OF ABANDONMENT

This application is abandoned in view of:

1. ☐ Applicant's failure to respond to the Office letter, mailed _____.
2. ☐ Applicant's letter of express abandonment which is in compliance with 37 C.F.R. 1.138.
3. ☐ Applicant's failure to timely file the response received _____ within the period set in the Office letter.
4. ☒ Applicant's failure to pay the required issue fee within the statutory period of 3 months from the mailing date of 08/05/97 of the Notice of Allowance.
   - ☐ The issue fee was received on _____.
   - ☐ The issue fee has not been received in Allowed Files Branch as of _____.

   In accordance with 35 U.S.C. 151, and under the provisions of 37 C.F.R. 1.316(b), applicant(s) may petition the Commissioner to accept the delayed payment of the issue fee if the delay in payment was unavoidable. The petition must be accompanied by the issue fee, unless it has been previously submitted, in the amount specified by 37 C.F.R. 1.17 (l), and a verified showing as to the causes of the delay.

   If applicant(s) never received the Notice of Allowance, a petition for a new Notice of Allowance and withdrawal of the holding of abandonment may be appropriate in view of Delgar Inc. v. Schuyler, 172 U.S.P.Q. 513.
5. ☐ Applicant's failure to timely correct the drawings and/or submit new or substitute formal drawings by _____ as required in the last Office action.
   - ☐ The corrected and/or substitute drawings were received on _____.
6. ☐ The reason(s) below.

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EXHIBIT K

Office Action Summary	Application No. 08/964,328	Applicant(s) SHERMAN, ET AL.
	Examiner JAMES M. SPEAR	Group Art Unit 1615

☒ Responsive to communication(s) filed on *Nov 5, 1997*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *THREE* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-18* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☒ Claim(s) *11, 13, and 14* is/are allowed.

☒ Claim(s) *1, 15, 17, and 18* is/are rejected.

☒ Claim(s) *2-10, 12, and 16* is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *6*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

EXHIBIT L

EXTENDED RELEASE FORMULATION

This application is a continuation -in-part of copending Application No. 08/821,137, filed March 20, 1997, which, in turn, claims priority from Provisional Application No. 60/014,006 filed March 25, 1996.

Background of the Invention

Extended release drug formulations are conventionally produced as compressed tablets by hydrogel tablet technology. To produce these sustained release tablet drug dosage forms, the active ingredient is conventionally compounded with cellulose ethers such as methyl cellulose, ethyl cellulose or hydroxypropylmethylcellulose with or without other excipients and the resulting mixture is pressed into tablets. When the tablets are orally administered, the cellulose ethers in the tablets swell upon hydration from moisture in the digestive system, thereby limiting exposure of the active ingredient to moisture. As the cellulose ethers are gradually leached away by moisture, water more deeply penetrates the gel matrix and the active ingredient slowly dissolves and diffuses through the gel, making it available for absorption by the body. An example of such a sustained release dosage form of the analgesic/antiinflammatory drug etodolac (Lodine®) appears in US patent 4,966,768. US patent 4,389,393 discloses sustained release therapeutic compressed solid unit dose forms of an active ingredient plus a carrier base comprised of a high molecular weight hydroxypropylmethylcellulose, methyl cellulose, sodium carboxymethylcellulose and or other cellulose ether.

Where the production of tablets is not feasible, it is conventional in the drug industry to prepare encapsulated drug formulations which provide extended or sustained release properties. In this situation, the extended release capsule dosage forms may be formulated by mixing the drug with one or more binding agents to form a uniform mixture which is then moistened with water or a solvent such as ethanol to form an extrudable plastic mass from which small diameter, typically 1 mm, cylinders of drug/matrix are extruded, chopped into appropriate lengths and transformed into spheroids using standard spheronization equipment. The spheroids, after drying, may then be film-coated to retard dissolution. Gelatin capsules are filled with the film-coated spheroids in the quantity needed to obtain the desired therapeutic effect. Spheroids releasing the drug at different rates may be combined in a gelatin capsule to obtain desired release rates and blood levels. US patent 4,138,475 discloses a sustained release pharmaceutical composition consisting of a hard gelatin capsule filled with film-coated spheroids comprised of propanolol in admixture with microcrystalline cellulose

wherein the film coating is composed of ethyl cellulose, optionally, with hydroxypropylmethylcellulose and/or a plasticizer.

Venlafaxine, 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol, is an important drug in the neuropharmacological arsenal used for treatment of depression. Venlafaxine and the acid addition salts thereof are disclosed in US patent 4,535,186. Venlafaxine hydrochloride is presently administered to adults in compressed tablet form in doses ranging from 75 to 350 mg/day , in divided doses two or three times a day. In therapeutic dosing with venlafaxine hydrochloride tablets, rapid dissolution results in a rapid increase in blood plasma levels of the active compound shortly after administration followed by a decrease in blood plasma levels over several hours as the active compound is eliminated or metabolized, until sub-therapeutic plasma levels are approached after about twelve hours following administration, thus requiring additional dosing with the drug. With the plural daily dosing regimen, the most common side effect is nausea, experienced by about forty five percent of patients under treatment with venlafaxine hydrochloride. Vomiting also occurs in about seventeen percent of the patients.

Brief Description of the Invention

In accordance with this invention, there is provided an extended release (ER), encapsulated formulation containing venlafaxine hydrochloride as the active drug component, which provides in a single dose, a therapeutic blood serum level over a twenty four hour period.

Through administration of the venlafaxine formulation of this invention, there is provided a method for obtaining a flattened drug plasma concentration to time profile, thereby affording a tighter plasma therapeutic range control than can be obtained with multiple daily dosing. In other words, this invention provides a method for eliminating the sharp peaks and troughs (hills and valleys) in blood plasma drug levels induced by multiple daily dosing with conventional immediate release venlafaxine hydrochloride tablets. In essence, the plasma levels of venlafaxine hydrochloride rise, after administration of the extended release formulations of this invention, for between about five to about eight hours (optimally about six hours) and then begin to fall through a protracted, substantially linear decrease from the peak plasma level for the remainder of the twenty four hour period, maintaining at least a threshold therapeutic level of the drug during the entire twenty-four period. In contrast, the conventional immediate release venlafaxine hydrochloride tablets give peak blood plasma levels in 2 to 4 hours.

Hence, in accordance with the use aspect of this invention, there is provided a method for moderating the plural blood plasma peaks and valleys attending the pharmacokinetic utilization of multiple daily tablet dosing with venlafaxine hydrochloride which comprises administering to a patient in need of treatment with venlafaxine hydrochloride, a one-a-day, extended release formulation of venlafaxine hydrochloride.

The use of the one-a-day venlafaxine hydrochloride formulations of this invention reduces by adaptation, the level of nausea and incidence of emesis that attend the administration of multiple daily dosing. In clinical trials of venlafaxine hydrochloride ER, the probability of developing nausea in the course of the trials was greatly reduced after the first week. Venlafaxine ER showed a statistically significant improvement over conventional venlafaxine hydrochloride tablets in two eight-week and one 12 week clinical studies. Thus, in accordance with this use aspect of the invention there is provided a method for reducing the level of nausea and incidence of emesis attending the administration of venlafaxine hydrochloride which comprises dosing a patient in need of treatment with venlafaxine hydrochloride with an extended release formulation of venlafaxine hydrochloride once a day in a therapeutically effective amount.

Detailed Description of the Invention

1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol hydrochloride is polymorphic. Of the forms isolated and characterized to date, Form I is considered to be the kinetic product of crystallization which can be converted to Form II upon heating in the crystallization solvent. Forms I and II cannot be distinguished by their melting points but do exhibit some differences in their infrared spectra and X-ray diffraction patterns. Any of the polymorphic forms such as Form I or Form II may be used in the formulations of the present invention.

The extended release formulations of this invention are comprised of 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride in admixture with microcrystalline cellulose and hydroxypropylmethylcellulose. Formed as beads or spheroids, the drug containing formulation is coated with a mixture of ethyl cellulose and hydroxypropylmethyl cellulose to provide the desired level of coating, generally from about two to about twelve percent on a weight/weight basis of final product or more preferably from about five to about ten percent (w/w) , with best results obtained at from about 6 to about 8 percent (w/w). More specifically, the extended release spheroid formulations of this invention comprise from about 30 to 40 percent

venlafaxine hydrochloride, from about 50 to about 70 percent microcrystalline cellulose, NF, from about 0.25 to about 1 percent hydroxypropylmethylcellulose, USP, and from about 5 to about 10 percent film coating, all on a weight/weight basis. And preferably, the spheroid formulations contain about 35 percent venlafaxine hydrochloride, about 55 to 60 percent microcrystalline cellulose NF (Avicel® PH101), about one half percent hydroxypropyl methylcellulose 2208 USP (K3, Dow, which has a viscosity of 3 cps for 2% aqueous solutions, a methoxy content of 19–24% and a hydroxypropoxy content of 4–13%), and from about 6 to 8 percent film coating.

The film coating is comprised of 80 to 90 percent of ethyl cellulose, NF and 10 to 20 percent hydroxypropyl methylcellulose (2910), USP on a weight/weight basis. Preferably the ethyl cellulose has a ethoxy content of 44.0–51% and a viscosity of 50 cps for a 5% aqueous solution and the hydroxypropylmethylcellulose is USP 2910 having a viscosity of 6 cps at 2% aqueous solution with a methoxy content of 28–30% and a hydroxypropoxy content of 7–12%. The ethyl cellulose used herein is Aqualon HG 2834.

Other equivalents of the hydroxypropylmethylcelluloses 2208 and 2910 USP and ethyl cellulose, NF, having the same chemical and physical characteristics as the proprietary products named above may be substituted in the formulation without changing the inventive concept. Important characteristics of suitable hydroxypropylmethylcelluloses include a low viscosity, preferably less than 10 cps and more preferably 2-5 cps, and a gel temperature above that of the temperature of the extrudate during extrusion. As explained below, these and other characteristics which enable the extrudate to remain moist and soft (pliable) are preferred for the hydroxypropylmethylcellulose. In the examples below, the extrudate temperature was generally 50-55°C.

It was completely unexpected that an extended release formulation containing venlafaxine hydrochloride could be obtained because the hydrochloride of venlafaxine proved to be extremely water soluble. Numerous attempts to produce extended release tablets by hydrogel technology proved to be fruitless because the compressed tablets were either physically unstable (poor compressibility or capping problems) or dissolved too rapidly in dissolution studies. Typically, the tablets prepared as hydrogel sustained release formulations gave 40-50% dissolution at 2 hrs, 60-70% dissolution at 4 hrs and 85-100% dissolution at 8 hrs.

Numerous spheroid formulations were prepared using different grades of microcrystalline cellulose and hydroxypropyl methylcellulose, different ratios of venlafaxine hydrochloride and filler, different binders such as polyvinylpyrrolidone,

methylcellulose, water, and polyethylene glycol of different molecular weight ranges in order to find a formulation which would provide a suitable granulation mix which could be extruded properly. In the extrusion process, heat buildup occurred which dried out the extrudate so much that it was difficult to convert the extruded cylinders into spheroids. Addition of hydroxypropylmethylcellulose 2208 to the venlafaxine hydrochloride–microcrystalline cellulose mix made production of spheroids practical.

The following examples are presented to illustrate applicant's solution to the problem of preparation of the extended release drug containing formulations of this invention.

Example 1.

VENLAFAXINE HYDROCHLORIDE EXTENDED RELEASE CAPSULES

A mixture of 44.8 parts (88.4 % free base) of venlafaxine hydrochloride, 74.6 parts of the microcrystalline cellulose, NF, and 0.60 parts of hydroxypropylmethyl cellulose 2208, USP, are blended with the addition of 41.0 parts water. The plastic mass of material is extruded, spheronized and dried to provide uncoated drug containing spheroids.

Stir 38.25 parts of ethyl cellulose, NF, HG2834 and 6.75 parts of hydroxypropyl methylcellulose 2910, USP in a 1:1 v/v mixture of methylene chloride and anhydrous methanol until solution of the film coating material is complete.

To a fluidized bed of the uncoated spheroids is applied 0.667 parts of coating solution per part of uncoated spheroids to obtain extended release, film coated spheroids having a coating level of 3%.

The spheroids are sieved to retain the coated spheroids of a particle size between 0.85 mm to 1.76 mm diameter. These selected film coated spheroids are filled into hard gelatin capsules conventionally.

Example 2.

Same as for Example 1 except that 1.11 parts of the film coating solution per part of uncoated spheroids is applied to obtain a coating level of 5%.

Example 3.

Same as for Example 1 except that 1.33 parts of the film coating solution is applied to 1 part of uncoated spheroids to obtain a coating level of 6%.

Example 4.

Same as for Example 1 except that 1.55 parts of the film coating solution is applied to 1 part of uncoated spheroids to obtain a coating level of 7%.

In the foregoing failed experiments and in Examples 1-4, the extrusion was carried out on an Alexanderwerk extruder. Subsequent experiments carried out on Hutt and Nica extruders surprisingly demonstrated that acceptable, and even improved, spheroids could be made without the use of an hydroxypropylmethyl cellulose.

In such further experiments the applicability of the invention was extended to formulations wherein the weight percentage of venlafaxine hydrochloride is 6% to 40%, preferably 8% to 35%. Thus, the extended release spheroid formulations of this invention comprise from about 6 to 40 percent venlafaxine hydrochloride, from about 50 to about 94 percent microcrystalline cellulose, NF, optionally, from about 0.25 to about 1 percent hydroxypropylmethylcellulose, and from about 2 to about 12 percent, preferably about 3 to 9 percent, film coating.

Spheroids of the invention were produced having 8.25% (w/w) venlafaxine hydrochloride and the remainder (91.75%, w/w) being microcrystalline cellulose, with a coating of from 3 to 5 % (w/w), preferably 4%, of the total weight. The spheroids with 8.25% venlafaxine hydrochloride and 4% coating were filled into No. 2 white opaque shells with a target fill weight of 236 mg.

Further spheroids of the invention were produced having 16.5% (w/w) venlafaxine hydrochloride and the remainder (83.5%,w/w) being microcrystalline cellulose, with a coating of from 4 to 6 % (w/w), preferably 5%, of the total weight. The spheroids 16.5% venlafaxine hydrochloride and 5% coating were filled into No. 2 white opaque shells with a target fill weight of 122 mg.

The test for acceptability of the coating level is determined by analysis of the dissolution rate of the finished coated spheroids prior the encapsulation.. The dissolution procedure followed uses USP Apparatus 1 (basket) at 100 rpm in purified water at 37°C.

Conformance with the dissolution rate given in Table 1 provides the twenty-four hour therapeutic blood levels for the drug component of the extended release capsules of this invention in capsule form. Where a given batch of coated spheroids releases drug too slowly to comply with the desired dissolution rate study, a portion of uncoated spheroids or spheroids with a lower coating level may be added to the batch to provide,

after thorough mixing, a loading dose for rapid increase of blood drug levels. A batch of coated spheroids that releases the drug too rapidly can receive additional film-coating to give the desired dissolution profile.

Table 1

Acceptable Coated Spheroid Dissolution Rates

Time (hours)	Average % Venlafaxine HCl released
2	<30
4	30-55
8	55-80
12	65-90
24	>80

Batches of the coated venlafaxine hydrochloride containing spheroids which have a dissolution rate corresponding to that of Table 1 are filled into hard gelatin capsules in an amount needed to provide the unit dosage level desired. The standard unit dosage immediate release (IR) tablet used presently provides amounts of venlafaxine hydrochloride equivalent to 25 mg, 37.5 mg, 50 mg, 75 mg and 100 mg venlafaxine. The capsules of this invention are filled to provide an amount of venlafaxine hydrochloride equivalent to that presently used in tablet form and also up to about 150 mg venlafaxine hydrochloride.

Dissolution of the venlafaxine hydrochloride ER capsules is determined as directed in the U. S. Pharmacopoeia (USP) using apparatus 1 at 100 rpm on 0.9 L of water. A filtered sample of the dissolution medium is taken at the times specified. The absorbance of the clear solution is determined from 240 to 450 nanometers (nm) against the dissolution medium. A baseline is drawn from 450 nm through 400 nm and extended to 240 nm. The absorbance at the wavelength of maximum absorbance (about 274 nm) is determined with respect to this baseline. Six hard gelatin capsules are filled with the theoretical amount of venlafaxine hydrochloride spheroids and measured for dissolution. Standard samples consist of venlafaxine hydrochloride standard solutions plus a gelatin capsule correction solution.

The percentage of venlafaxine released is determined from the equation

$$\% \text{ Venlafaxine hydrochloride released} = \frac{(As)(Wr)(S)(V1)(0.888)(100)}{(Ar)(V2)(C)}$$

where As is absorbance of sample preparation, Wr is weight of reference standard, mg; S is strength of the reference standard; decimal; V1 is the volume of dissolution medium used to dissolve the dosage form, mL; 0.884 is the percent free base, Ar is the absorbance of the standard preparation, V2 is the volume of reference standard solution, mL; and C is the capsule claim in mg.

Table 2 shows the plasma level of venlafaxine versus time for one 75 mg conventional Immediate Release (IR) tablet administered every 12 hours, two 75 mg extended release (ER) capsules administered simultaneously every 24 hours, and one 150 mg extended release (ER) capsule administered once every 24 hours in human male subjects. The subjects were already receiving venlafaxine hydrochloride according to the dosage protocol, thus the plasma blood level at zero time when dosages were administered is not zero.

[Text continues with Table 2 on next page]

Table 2

Plasma venlafaxine level (ng/mL) versus time, conventional tablet (not extended release) versus ER capsule

Time (hours)	75 mg (IR)tablet (q 12 h)	2 x 75 mg (ER)capsules (q 24 hr)	1 x 150 mg (ER)capsules (q 24 h)
0	62.3	55.0	55.8
0.5	76.3		
1	135.6	53.3	53.2
2	212.1	69.8	70.9
4	162.0	138.6	133.3
6	114.6	149.0	143.5
8	86.7	129.3	129.5
10		118.4	114.4
12	51.9	105.1	105.8
12.5	74.7		
13	127.5		
14	161.3	90.5	91.3
16	134.6	78.2	78.5
18	106.2		
20	83.6	62.7	63.3
24	57.6	56.0	57.3

Table 2 shows that the plasma levels of two 75 mg/capsule venlafaxine hydrochloride ER capsules and one 150 mg/capsule venlafaxine hydrochloride ER capsule provide very similar blood levels. The data also show that the plasma level after 24 hours for either extended release regimen is very similar to that provided by two immediate release 75 mg tablets of venlafaxine hydrochloride administered at 12 hour intervals.

Further, the plasma levels of venlafaxine obtained with the extended release formulation do not increase to the peak levels obtained with the conventional immediate

release tablets given 12 hours apart. The peak level of venlafaxine from (ER) , somewhat below 150 ng/ml, is reached in about six hours, plus or minus two hours, based upon this specific dose when administered to patients presently under treatment with venlafaxine hydrochloride (IR). The peak plasma level of venlafaxine, somewhat over 200 ng/ml, following administration of (IR) is reached in two hours and falls rapidly thereafter.

Table 3 shows venlafaxine blood plasma levels in male human subjects having a zero initial blood plasma level. Again, a peak blood plasma concentration of venlafaxine is seen at about 6 hours after dosing with venlafaxine hydrochloride extended release capsules in the quantities indicated. The subjects receiving the single 50 mg immediate release tablet showed a peak plasma level occurring at about 4 hours. For comparative purposes, the plasma levels of venlafaxine for subjects receiving the conventional formulated tablet can be multiplied by a factor of three to approximate the plasma levels expected for a single dose of 150 mg. conventional formulation.

Table 3.

Plasma Blood Levels in Human Males Having No Prior Venlafaxine Blood Level

Time (Hours)	1 x 50 mg IR tablet	2 x 75 mg ER capsules	1 x 150 mg ER capsule
0	0	0	0
1	27.87	1.3	0
1.5	44.12	6.0	2.2
2	54.83	20.6	12.8
4	66.38	77.0	81.0
6	49.36	96.5	94.4
8	30.06	93.3	86.9
10	21.84	73.2	72.8
12	15.91	61.3	61.4
14	13.73	52.9	51.9
16	10.67	47.5	41.1
20	5.52	35.2	34.0
24	3.56	29.3	28.5
28	2.53	23.4	22.9
36	1.44	11.9	13.5
48	0.66	5.8	5.2

The blood plasma levels of venlafaxine were measured according to the following procedure. Blood samples from the subjects were collected in heparinized evacuated blood tubes and the tubes were inverted gently several times. As quickly as possible, the tubes were centrifuged at 2500 rpm for 15 minutes. The plasma was pipetted into plastic tubes and stored at -20°C until analysis could be completed.

To 1 mL of each plasma sample in a plastic tube was added 150 µL of a stock internal standard solution (150 µg/ml). Saturated sodium borate (0.2 mL) solution was added to each tube and vortexed. Five mL of ethyl ether was added to each tube which were then capped and shaken for 10 minutes at high speed. The tubes were centrifuged at 3000 rpm for 5 minutes. The aqueous layer was frozen in dry ice and the organic layer transferred to a clean screw cap tube. A 0.3 mL portion of 0.01 N HCl solution was added to each tube and shaken for 10 minutes at high speed. The aqueous layer was frozen and the organic layer removed and discarded. A 50µL portion of the mobile phase (23:77 acetonitrile:0.1M monobasic ammonium phosphate buffer, pH 4.4) was added to each tube, vortexed, and 50 µL samples were injected on a Supelco Supelcoil LC-8-DB, 5 cm x 4.6 mm, 5 µ column in a high pressure liquid chromatography apparatus equipped with a Waters Lambda Max 481 detector or equivalent at 229 nm. Solutions of venlafaxine hydrochloride at various concentrations were used as standards.

Thus, the desired dissolution rate of a sustained release dosage form of venlafaxine hydrochloride, impossible to achieve with hydrogel tablet technology, has been achieved with the film-coated spheroid compositions of this invention.

What is claimed is:

1. An encapsulated, extended release formulation of venlafaxine hydrochloride comprising a hard gelatin capsule containing a therapeutically effective amount of venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and, optionally, hydroxypropylmethylcellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose.

2. An extended release formulation according to claim 1 wherein the spheroids are comprised of about 30% to 40% venlafaxine hydrochloride by weight, about 50% to about 70% microcrystalline cellulose, NF, by weight, and from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

3. An encapsulated, extended release formulation of venlafaxine hydrochloride according to claim 1 having the following dissolution profile in USP Apparatus 1 (basket) at 100 rpm in purified water at 37°C:

Time (hours)	Average % Venlafaxine HCl released
2	<30
4	30-55
8	55-80
12	65-90
24	>80

4. An extended release formulation according to claim 2 wherein the spheroids are composed of about 37% by weight of venlafaxine hydrochloride, about 0.5% by weight of hydroxypropylmethylcellulose 2208, and about 62% by weight of microcrystalline cellulose.

5. A composition according to claim 2 wherein the film coating is comprised of ethyl cellulose (4.81% of total weight) and hydroxypropylmethylcellulose (0.85% of total weight).

Sub A2

6. A composition according to claim 2 wherein the film coating comprises 6- 8% by weight of total weight.

7. A composition according to claim 2 wherein the film coating is comprised of ethyl cellulose (2.48% of total weight) and hydroxypropylmethylcellulose (0.437% of total weight).

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8. A composition according to claim 2 wherein the film coating composition is comprised of ethyl cellulose having a 44.0-51.0% content of ethoxy groups and hydroxypropylmethylcellulose having a methoxy content of 28.0-30.0% and a hydroxypropoxy group content of 7.0-12.0%.

9. A film coating composition according to claim 7 which is comprised of about 85% by total weight of film coating of ethyl cellulose having a 44.0-51.0% content of ethoxy groups, and about 15% by total weight of film coating of hydroxypropylmethylcellulose having a methoxy content of 28.0-30.0% and a hydroxypropoxy group content of 7.0-12.0%.

10. A film coating composition according to claim 7 which is comprised of 85% by weight of ethyl cellulose type HG 2834 and 15% by weight of hydroxypropylmethylcellulose type 2910.

Sub A4

11. An extended release formulation of venlafaxine hydrochloride for once daily administration which comprises spheroids containing 37.3% venlafaxine, 62.17% microcrystalline cellulose and 0.5% hydroxypropylmethylcellulose type 2208, coated with a quantity of a mixture comprised of 85% ethyl cellulose type HG 2834 and 15% hydroxypropyl-methylcellulose type 2910 sufficient to give coated spheroids having a dissolution profile which gives the desired release rate over a 24 hour period.

12. An extended release formulation of venlafaxine hydrochloride according to claim 7 which provides peak serum levels of up to 150 ng/ml and extended therapeutically effective plasma levels over a twenty four hour period.

13. A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty four hour period with diminished incidences of nausea and emesis which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about four to about eight hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

14. A method for eliminating the troughs and peaks of drug concentration in a patients blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride which comprises administering orally to a patient in need thereof, an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about four to about eight hours, said formulation containing venlafaxine hydrochloride as the active ingredient.

Sub A4 15. An extended release formulation according to claim 1 wherein the spheroids are comprised of about 6% to 40% venlafaxine hydrochloride by weight, about 50% to about 940% microcrystalline cellulose, NF, by weight, and, optionally, from about 0.25% to about 1% by weight of hydroxypropylmethylcellulose, USP, and coated with from about 2% to about 12% of total weight of film coating comprised of from about 80% to about 90% by weight of film coating of ethyl cellulose, NF, and from about 10% to about 20% by weight of film coating of hydroxypropylmethylcellulose, USP.

16. An encapsulated, extended release formulation of venlafaxine hydrochloride according to claim 15 having the following dissolution profile in USP Apparatus 1 (basket) at 100 rpm in purified water at 37°C:

Time (hours)	Average % Venlafaxine HCl released
2	<30
4	30-55
8	55-80
12	65-90
24	>80

Sub A4

17. An extended release formulation according to claim 14 wherein the spheroids are composed of about 8.25% by weight of venlafaxine hydrochloride and about 91.75% by weight of microcrystalline cellulose, with a coating of from 3 to 5 % by weight of the total weight.

18. An extended release formulation according to claim 14 wherein the spheroids are composed of about 16.5% by weight of venlafaxine hydrochloride and about 83.5% by weight of microcrystalline cellulose, with a coating of from 4 to 6 % by weight of the total weight.

Add A5

ABSTRACT

EXTENDED RELEASE FORMULATION

This invention relates to a 24 hour extended release dosage formulation and unit dosage form thereof of venlafaxine hydrochloride, an antidepressant, which provides better control of blood plasma levels than conventional tablet formulations which must be administered two or more times a day and further provides a lower incidence of nausea and vomiting than the conventional tablets.

EXHIBIT M

(12) **United States Patent**
Oosterbaan et al.

(10) **Patent No.: US 6,696,496 B2**
(45) **Date of Patent: Feb. 24, 2004**

(54) **LOW WATER-SOLUBLE VENLAFAXINE SALTS**

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(57) **ABSTRACT**

Low water soluble salts of venlafaxine, especially venlafaxine maleate, are provided. Such salts can provide a variety of dosage forms including hydrogel-based extended release dosage forms.

25 Claims, No Drawings

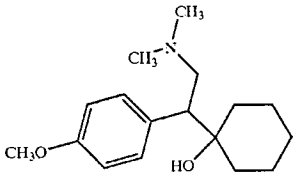
LOW WATER-SOLUBLE VENLAFAXINE SALTS

This application claims the benefit of priority under 35 U.S.C. §119 from U.S. provisional application serial No. 60/367,704, filed Mar. 28, 2002 and from U.S. provisional application serial No. 60/372,447, filed Apr. 16, 2002; the entire contents of each application being incorporated herein by reference.

BACKGROUND OF THE INVENTION

The present invention relates to low water-soluble venlafaxine salts, especially venlafaxine maleate, various forms thereof, and the use of the same in pharmaceutical compositions for treating depression and other conditions.

Venlafaxine is the common name for the compound 1-[2-(dimethylamino)-1-(4-methoxyphenyl) ethyl] cyclohexanol, having the structure shown below.



U.S. Pat. No. 4,535,186 describes a class of hydroxycycloalkanephenethyl amines as being useful antidepressants and exemplifies the compound now known as venlafaxine hydrochloride as one of the suitable species. Venlafaxine hydrochloride is approved for sale in various countries including the United States of America. It is available as an immediate release tablet and as an extended release capsule, under the brand name EFFEXOR® (Wyeth Ayerst) and EFFEXOR XR® (Wyeth Ayerst) respectively.

Venlafaxine has been the subject of various research endeavors. For example, U.S. Pat. No. 5,043,466 describes a process for making cyclohexanol derivatives in a specified solvent composition. Example 3 of this patent shows the synthesis of venlafaxine as the hydrochloride salt thereof.

U.S. Pat. No. 6,274,171 and related EP 0 797 991A1 disclose encapsulated extended release formulations for venlafaxine hydrochloride. These patents indicate that commercial venlafaxine hydrochloride tablets were administered two or three times daily, but that due to variations in the drug concentration in the patient's blood plasma caused by such a dosing regimen, unwanted side effects, especially nausea and vomiting were common. A once daily, encapsulated extended release dosage form is disclosed that provides a flattened drug plasma profile and reduces these side effects. The encapsulated dosage form is taught to comprise spheroids of venlafaxine hydrochloride, microcrystalline cellulose, and hydroxypropylmethylcellulose (HPMC). These spheroids are coated with a mixture of ethyl cellulose and HPMC. By providing an appropriate amount of the coating, the desired blood plasma profile can be obtained. An acceptable batch of coated spheroids will meet the following in vitro dissolution profile:

Time (hours)	Average % venlafaxine hydrochloride released
2	<30
4	30–55
8	55–80
12	65–90
24	>80

using USP Apparatus 1 (basket) at 100 rpm in purified water at 37° C. The coated spheroids can be from a single batch or represent a blend of different batches.

U.S. Pat. No. 6,274,171 and EP 0 797 991 also state that forming an extended release dosage form of venlafaxine hydrochloride was difficult in part due to the high water solubility of the hydrochloride salt. In fact, these patents disclose that "[n]umerous attempts to produce extended release tablets by hydrogel technology proved to be fruitless because the compressed tablets were either physically unstable (poor compressibility or capping problems) or dissolved too rapidly in dissolution studies." See U.S. Pat. No. 6,274,171 at column 4, lines 60–65 and EP 0 797 991 at page 3 lines 35–37. Unlike the encapsulated extended release formulations described in these patents, a hydrogel extended release venlafaxine hydrochloride tablet is taught to typically exhibit a dissolution profile wherein 40%–50% is released at 2 hours, 60%–70% is released at 4 hours, and 85%–100% is released at 8 hours.

WO99/22724 also discloses encapsulated venlafaxine hydrochloride extended release dosage forms. These formulations differ from those in U.S. Pat. No. 6,274,171 and EP 0 797 991 in that the spheroid is substantially free of HPMC. Apparently HPMC can be omitted from the spheroid when smaller amounts of venlafaxine hydrochloride are employed.

U.S. Pat. No. 6,197,828 and WO00/32556 discloses the use of individual (+) and (−) enantiomers, respectively, of venlafaxine as well as metabolites thereof. While the commercial venlafaxine hydrochloride is a racemate, these patents teach that various side effects may be reduced by using one isomer substantially without the presence of the other.

Although venlafaxine hydrochloride provides good pharmaceutical activity, it would be beneficial to find other forms of venlafaxine. In particular, venlafaxine forms that are easier handle would be advantageous. Venlafaxine hydrochloride is relatively aggressive towards handling equipment and is irritating to the skin, etc. of human personnel that handle the pure active. A venlafaxine form that is less aggressive and less irritating would be desirable. It is further desirable to provide a venlafaxine form that can be easily formulated into various dosage forms including hydrogel extended release tablets.

SUMMARY OF THE INVENTION

The present invention is based on the discovery of low water-soluble venlafaxine salts. Unlike venlafaxine hydrochloride, the low water-soluble salts of the present invention are more easily formulated into extended release formulations including hydrogel tablets. Thus, a first aspect of the present invention relates to a low water-soluble venlafaxine salt. Such salts exhibit lower water-solubility relative to venlafaxine hydrochloride and preferably 380 mg/ml or less.

A preferred low water-soluble venlafaxine salt is venlafaxine maleate. Accordingly, a second aspect of the inven-

tion relates to a venlafaxine maleate compound. The compound can be isolated and/or purified or it can be part of a composition. The compound can be in solid form including crystalline forms but is not limited thereto. A preferred compound is crystalline venlafaxine hydrogenmaleate anhydrate.

Another aspect of the present invention relates to a pharmaceutical composition comprising an effective amount of venlafaxine maleate and a pharmaceutically acceptable excipient. The composition can be an immediate release dosage form or an extended release dosage form and embraces tablets as well as pellets/beads/spheroids or other encapsulated forms. In one embodiment, the venlafaxine maleate is provided in a hydrogel tablet. The hydrogel tablet preferably provides sufficient extended release so that the tablet is a once daily dosage form.

An additional aspect of the present invention relates to a pharmaceutical composition comprising a low water-soluble venlafaxine salt and a hydrophilic matrix material. Such a composition includes finished hydrogel tablets as well as tabletting powder blends and other intermediates in making a final dosage form. The hydrogel tablet exhibits extended release such that no more than twice daily dosing and preferably once daily dosing can be achieved.

A further aspect of the invention relates to the use of a low water-soluble venlafaxine salt, and in particular venlafaxine maleate, in treating venlafaxine-treatable diseases or conditions. Hence the invention provides a method for treating a venlafaxine-treatable disease or condition, which comprises administering to a patient in need thereof an effective amount of a low water-soluble venlafaxine salt such as venlafaxine maleate. The low water-soluble salt is typically administered as an oral composition such as a tablet or capsule and is preferably administered once daily.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is based on the surprising discovery that various salts of venlafaxine are low water-soluble relative to the water solubility of venlafaxine hydrochloride. As used herein "low water-soluble" venlafaxine salt means that the salt exhibits a water solubility that is less than two thirds the water solubility of venlafaxine hydrochloride, preferably less than half, more preferably one third and more preferably less than one quarter the water solubility of venlafaxine hydrochloride. In absolute values, a low water-soluble salt of venlafaxine preferably has a water solubility of 380 mg/ml or less, preferably 200 mg/ml or less, more preferably 150 mg/ml or less.

Such low water soluble salts include venlafaxine maleate compounds and venlafaxine benzenesulfonate (besylate) compounds and is expected to also include venlafaxine fumarate compounds, but is not limited thereto. Any salt of venlafaxine that exhibits a solubility within the above range is included within the meaning of low water soluble salts. Venlafaxine besylate compounds are more fully described in U.S. provisional patent application serial No. 60/367,734, filed Mar. 28, 2002, entitled "Venlafaxine Besylate," the entire contents of which are incorporated herein by reference. For simplicity, the present invention will be described with reference to a venlafaxine maleate compound, but it should be understood that it equally applies to all low water-soluble venlafaxine salts.

A venlafaxine maleate compound is any form of the salt formed by venlafaxine and maleic acid. Typically the venlafaxine and maleate moieties are present in about a 1:1 molar ratio, which is referred to herein as "venlafaxine hydrogenmaleate." However, other ratios such as 2:1 or 3:2 are also possible due to the fact that maleic acid contains two acid groups, each having the potential to from a salt with a venlafaxine moiety. In addition, venlafaxine maleate is less aggressive, less irritating, and easier to handle than venlafaxine hydrochloride. Note that maleic acid is generally easier to handle than hydrochloric acid. Accordingly, venlafaxine maleate is easier to formulate into a variety of dosage forms, especially extended release dosage forms, than venlafaxine hydrochloride. The preferred form is the venlafaxine hydrogenmaleate.

Venlafaxine maleate compounds are low-water soluble venlafaxine salts. For example, venlafaxine hydrogenmaleate anhydrate exhibits a water solubility of about 370 mg/ml, i.e. 368 mg/ml, while venlafaxine hydrochloride exhibits a water solubility of about 570 mg/ml at ambient conditions.

The venlafaxine in the venlafaxine maleate compound of the present invention can be any form of venlafaxine. For example, venlafaxine has one optically active carbon, thus allowing for existence of two enantiomers and a racemate. Both enantiomers are pharmaceutically active. The venlafaxine maleate compound can be based on the racemate or mixture of enantiomers of venlafaxine or on the pure or substantially pure (+) or (−) enantiomer of venlafaxine (hereinafter referred to as (+)-venlafaxine maleate and (−)-venlafaxine maleate): all are included within the meaning of "venlafaxine maleate" unless specifically noted otherwise.

The compound can be in isolated and/or purified form, but such is not required. The compound includes various physical forms of the salt including dissolved forms, oil or liquid forms, and solid forms including amorphous and crystalline forms.

The compound is typically in a crystalline form. Crystalline forms include venlafaxine maleate anhydrates, hydrates, and solvates. Preferably the venlafaxine maleate is venlafaxine maleate anhydrate, more preferably venlafaxine hydrogenmaleate anhydrate.

A venlafaxine maleate compound can be prepared by contacting a venlafaxine substrate with a maleate substrate. Typically the contacting occurs in a suitable solvent system. The venlafaxine maleate product can be isolated, if desired, by precipitation, evaporation, spray drying, or other conventional techniques known in the art.

The "venlafaxine substrate" includes any substance that provides a venlafaxine moiety or ion thereof and specifically includes racemic and enantiomeric venlafaxine base, a venlafaxine salt other than venlafaxine maleate, e.g. venlafaxine HCl, or a raw venlafaxine, i.e. a reaction product or reaction mixture comprising venlafaxine that has been obtained after the last step of production of venlafaxine. The venlafaxine substrate can be obtained by conventional processes and synthesis schemes known in the art. For example, U.S. Pat. Nos. 4,535,186, 5,043,466, and 6,197,828 all teach methods for making venlafaxine. Venlafaxine base in its isolated state is obtainable by neutralization of venlafaxine hydrochloride, extraction by ethyl acetate and evaporation of the solvent, according to the method disclosed in U.S. Pat. No. 6,197,828 and WO 00-32566. Alternatively, venlafaxine base can be obtained as a precipitate, preferably a filtratable precipitate, by the use of a contrasolvent, e.g. heptane, optionally with cooling and/or solvent removal, without the need to convert to a salt, as is more fully described in U.S. provisional patent application serial No. 60/367,736, filed Mar. 28, 2002, entitled "Venlafaxine Free Base," the entire contents of which are incorporated herein by reference.

Single enantiomers of venlafaxine free base can be made as described in J.Med.Chem. 1990, 33 (10), 2899–2905. Venlafaxine hydrochloride is commercially available and can be produced according to U.S. Pat. No. 4,535,186, EP 112669, U.S. Pat. Nos. 5,043,466, 6,197,828 and WO 01-07397. Other salts can be formed by methods analogous to those disclosed in these cited patent documents.

The "maleate substrate" includes any substance that provides a maleic acid moiety or ion thereof and specifically includes any form of maleic acid as well as a salt of maleic acid with a base. A preferred substrate is maleic acid. Maleate substrates are commercially available and/or may be prepared by methods known in the prior art.

The molar ratio of the substrates is not particularly limited and is generally about stoichiometric to the desired ratio. Typically a slight excess of maleate substrate is used. Commonly the molar ratio of venlafaxine substrate to maleate substrate is within the range of 0.8:1 to 1.2:1, more typically 0.9:1 to 1.1:1 or about 1:1. However, up to a significant excess of one substrate, especially the maleate substrate can be used. Such excess of either maleate or venlafaxine is typically in the range of 1.1 to 3.0:1, more typically 1.1 to 2:1. For economy reasons, excesses are normally kept small and typically the excess maleate substrate, if any, is provided in slight stoichiometric excess such as 1.01 to 1.5 times the molar amount of venlafaxine.

The solvent system is preferably selected so as to facilitate the salt reaction and to allow subsequent separation of the resulting maleate. Advantageously, both venlafaxine substrate and the maleate substrate are dissolvable in the solvent system, at least at elevated temperatures. In the process, a mixture, slurry, or solution of venlafaxine substrate and a solvent may be contacted with a maleate substrate, or conversely, a mixture, slurry, or solution of maleate substrate and a solvent may be contacted with venlafaxine substrate. In another embodiment, both partners may be combined with a solvent system prior to being contacted together, whereby the solvent system used for maleate substrate may be identical with or different from the solvent system used for the venlafaxine substrate. The solvent system can be comprised of a single solvent or a mixture of solvents. When two or more solvents are used, a two phase reaction scheme may be used wherein the venlafaxine substrate and maleate substrate are primarily reacted in one phase and the resulting venlafaxine maleate compound is primarily present in the other phase due to, inter alia, solubility differences, etc. Suitable solvents include water, a lower alcohol (C_1–C_6) such as methanol or ethanol, an aliphatic ketone such as acetone, an ether such as dioxane, an ester such as ethyl acetate, and mixtures thereof.

The temperature of contact of both substrates in the solvent system is from ambient to the boiling point of the solvent system, the later being preferred. It is not required that a complete solution is formed in this step, i.e. a slurry or two phase solution are also possible, though a single solution is generally preferred.

The venlafaxine maleate compound can be isolated or recovered from the salt forming reaction by any convenient means. For example, the venlafaxine maleate compound can be precipitated out of a solution or reaction mixture. The precipitation may be spontaneous depending upon the solvent system used and the conditions. Alternatively, the precipitation can be induced by reducing the temperature of the solvent, especially if the initial temperature at contact is elevated. The precipitation may also be facilitated by reducing the volume of the solution/solvent or by adding a contra solvent, i.e. a liquid miscible with the solvent in which the venlafaxine maleate is less soluble. Seed crystals of venlafaxine maleate may also be added to help induce precipitation. The precipitated venlafaxine maleate compound can be isolated by conventional methods such as filtration or centrifugation, optionally washed and dried, preferably under diminished pressure.

Alternatively, the venlafaxine maleate compound can be isolated by evaporating away the solvent and collecting the residue. Such a method generally leads to an oil or solid amorphous form of venlafaxine maleate. Similarly, an amorphous solid form of the venlafaxine maleate compound can be recovered by spray drying or freeze drying a solution containing the venlafaxine maleate compound.

In a preferred mode, venlafaxine base is dissolved in acetone under heating, maleic acid is added to the solution under stirring, the mixture is heated to complete dissolution and the clear solution is allowed to cool. Venlafaxine maleate anhydrate crystallizes from the solution and is separated by filtration and dried.

Venlafaxine maleate prepared in solid state may be, if necessary, purified to the desired degree of purity. Venlafaxine maleate can be purified for instance by a (re) crystallization from a suitable solvent that may be identical or different from the solvent system used for its production. Examples of preferred suitable solvents for a purifying crystallization step are acetone, ethanol, water, and combinations thereof.

Single enantiomers of venlafaxine maleate may be prepared essentially as disclosed above, whereby the venlafaxine substrate comprises the single enantiomer of venlafaxine. Preferred substrates are single enantiomers of venlafaxine base or venlafaxine hydrochloride.

The venlafaxine maleate compound of the present invention can be formulated with a pharmaceutically acceptable excipient into a pharmaceutical composition. The pharmaceutical compositions of the present invention include the unit dosage form as well as the intermediate bulk formulations such as pellets, beads, powder blends, etc. Typically the composition is a finished dosage form also referred to as a unit dose. Dosage forms include oral dosage forms, topical dosage forms such as a transdermal patch, parenteral dosage forms such as an injectable solution, and rectal dosage forms such as a suppository, but is not limited thereto. Oral dosage forms are the most preferred due to the ease of administration and include solid oral dosage forms such as capsules, tablets, sachets/granules, and powders, as well as liquid oral dosage forms such as solutions, suspensions, and emulsions.

Pharmaceutically acceptable excipients are well known in the art and include diluents, fillers, binders, lubricants, disintegrants, glidants, colorants, pigments, taste masking agents, sweeteners, plasticizers, and any acceptable auxiliary substances such as absorption enhancers, penetration enhancers, surfactants, co-surfactants, and specialized oils. The proper excipient(s) are selected based in part on the dosage form, the intended mode of administration, the intended release rate, and manufacturing reliability. Examples of common types of excipients include various polymers, waxes, calcium phosphates, and sugars. Polymers include cellulose and cellulose derivatives such as HPMC, hydroxypropyl cellulose, hydroxyethyl cellulose, microcrystalline cellulose, carboxymethylcellulose, sodium carboxymethylcellulose, calcium carboxymethylcellulose, and ethylcellulose; polyvinylpyrrolidones; polyethylenoxides; and polyacrylic acids including their copolymers and crosslinked polymers thereof, i.e. Carbopol® (B. F.

Goodrich), Eudragit® (Rohm), polycarbophil and chitosan polymers. Waxes include white beeswax, microcrystalline wax, carnauba wax, hydrogenated castor oil, glyceryl behenate, glycerylpalmito stearate, saturated polyglycolyzed glycerate. Calcium phosphates include dibasic calcium phosphate, anhydrous dibasic calcium phosphate, and tribasic calcium phosphate. Sugars include simple sugars such as lactose, maltose, mannitol, fructose, sorbitol, sacarose, xylitol, isomaltose, and glucose as well as complex sugars (polysaccharides) such as maltodextrin, amylodextrin, starches, and modified starches.

Any form of the venlafaxine maleate can be used in the pharmaceutical composition. Preferred venlafaxine maleate forms are: crystalline venlafaxine hydrogenmaleate anhydrate, (+)-venlafaxine maleate anhydrate, and (−)-venlafaxine maleate anhydrate. The amount of venlafaxine maleate compound contained in a unit dosage form is an amount effective to treat one or more venlafaxine-treatable diseases or conditions as is hereinafter defined and can be determined by workers skilled in the art without undue experimentation. Generally this amount ranges from 2 mg to 300 mg. For oral dosage forms the amount is generally from 30 mg to 300 mg per unit dose. Contemplated doses include amounts of about 37.5 mg, 75 mg, 100 mg, 112.5 mg, 150 mg, 200 mg, and 300 mg strengths. For clarity, all amounts of venlafaxine maleate are expressed herein in terms of the weight of the free base contained in the venlafaxine maleate compound, as is conventional in the art.

As mentioned above, oral dosage forms are preferred and include tablets, capsules, sachets/granules, and powders. Tablets can be soluble tablets, dispersible tablets, effervescent tablets, chewable tablets, lyophilized tablets, coated tablets including sugar coatings, enteric coatings, and gastro-soluble coatings, and modified release tablets including microencapsulated active substance tablets, matrix tablets, and coated tablets such as polymer coated extended release tablets and osmotic tablets of the mono-compartmental or bi-compartmental type. Capsules include hard gelatin capsules that can be filled with powder, pellets, granules, small tablets or mini-tablets. The capsule and/or the material placed within can be coated such as for enteric release or modified release. Soft capsules are also included and are more typically filled with liquids or dispersions, but are not limited thereto. Sachets or granules can be effervescent granules, coated granules, enteric granules, or modified release granules.

One embodiment of the present invention relates to an immediate release tablet. An "immediate release" as used herein means that at least 80% of the venlafaxine maleate in the tablet is dissolved by 30 minutes under a dissolution test using USP Apparatus 1 (basket) at 100 rpm in purified water at 37° C. Any conventional immediate release composition can be used in formulating the venlafaxine maleate immediate release tablet. Typically such tablets contain one or more binders and/or diluents such as HPMC, microcrystalline cellulose, a calcium phosphate, lactose, and mannitol; a lubricant such as magnesium stearate; and optionally a disintegrant such as sodium starch glycollate, crosscarmellose or crosspovidone. Additional excipients such as colorants, antioxidants, etc can also be present.

More preferably, however, the solid oral dosage form is an extended release dosage form. This can be accomplished in either a tablet or a capsule form. An extended release dosage form as used herein means that in a dissolution test using USP Apparatus 1 (basket) at 100 rpm in purified water at 37° C., less than 80% of the venlafaxine maleate is dissolved during the first two hours, more typically less than 50%, and preferably less than 30% of the venlafaxine maleate is dissolved during the first two hours. Extended release tablets or capsules generally allow for twice a day, or more preferably once a day dosing, to provide 24 hour therapeutic blood plasma levels of venlafaxine to the patient. In this regard, the most preferred dosage form is one which provides once daily dosing. Such a composition should meet the following in vitro dissolution profile:

Time (hours)	Average % venlafaxine maleate released
2	<30
4	30–55
8	55–80
12	65–90
24	>80

using USP Apparatus 1 (basket) at 100 rpm in purified water at 37° C. Most advantageously the extended release dosage from meets the above dissolution profile also in 0.1 N HCl aqueous solution.

In terms of in vivo performance, the extended release venlafaxine maleate pharmaceutical composition according to the present invention preferably exhibits on average a maximum venlafaxine blood plasma level not earlier than 4 hours, more preferably not earlier than 6 hours after administration of the composition. Typically the average peak plasma level is reached between 4 and 10 hours, more preferably between 6 and 8 hours after administration. In this regard, a preferred composition is bioequivalent to the commercially available EFFEXOR XR®.

Extended release tablets can be formulated according to any of the known techniques such as those based on matrix technology, osmotic pressure technology, multiparticulates compressed into tablets, multilayer tablets having at least one layer based on one of the foregoing, as well as coated tablets, using known materials and methods.

Tablets employing a matrix, in either a monolithic tablet or in one or more layers optionally built on a tablet core, are generally the most common and frequently the easiest to form from a commercial manufacturing standpoint. The matrix provides a diffusion and/or erosion release of the drug. The matrix is generally composed of at least one type of matrix material selected from hydrophilic (hydrogel), inert, lipophilic, and biodegradable matrix materials. Materials used for each of these kinds of matrices in pharmaceutical oral dosage forms are well known in the art and are briefly described below.

A hydrophilic matrix material is generally a polymeric material that swells upon contact with water to form a diffusion barrier. Suitable materials include cellulose derivatives such as methylcelluloses (i.e. having a viscosity of 400 cP to 4000 cP), hydroxyethylcellulose, HPMC, and sodium carboxymethyl cellulose; polysaccharides such as galactomannanes, potassium alginates, sodium alginates, agar-agar, carrageen, arabic gum, and sterculia gum; polyacrylates such as CARBOPOL 934, EUDRAGIT LD 35; Noveon or polycarbophils; and other water swellable polymers such as polyvinyl alcohol.

Inert matrix materials provide a tortuous path for the drug to escape the dosage form thereby controlling diffusion of the drug. Such materials include ethylcellulose (ETHOCEL).

Lipophilic matrix materials work through a combination of erosion and diffusion. Examples of lipophilic materials include glyceryl palmitosterate (PRECIROL ATO 5), glyc-

eryl behenate (COMPRITOL 888 ATO) and Hydrogenated castor oil (CUTINA HR).

Biodegradable matrix materials also operate through a combination of erosion and diffusion. Biodegradable materials include, for example, polyesters of lactic acid and glycolic acid, polyorthoesters, polyanhydrides and caprolactones. A further description of this technology is set forth in WO02/11701, WO92/04013, and EP 1 005 863.

Because venlafaxine maleate has a surprisingly lower water solubility than venlafaxine hydrochloride, venlafaxine maleate can be more readily formulated into conventional extended release forms including hydrogel tablets. Surprisingly, venlafaxine maleate can even be formulated into a once-a-day extended release hydrogel tablet. A "hydrogel tablet" is one that contains a hydrophilic matrix material that swells or "gels" upon contact with water to thereby slow the diffusion release of the active ingredient. Any of the above-described hydrophilic matrix materials can be used in forming venlafaxine maleate hydrogel tablets of the present invention.

Preferably a hydrogel tablet of the present invention comprises 10%–50% of a venlafaxine maleate compound, preferably a monohydrate form, and 30% to 75% of a hydrogel-forming agent, preferably an HPMC. In some embodiments it may be advantageous for the weight ratio of venlafaxine maleate to hydrogel-forming agent to be in the range of 0.8–1.2:1, preferably approximately 1:1, respectively. In addition to the venlafaxine maleate and hydrogel-forming agent, the composition may further comprise other suitable inert ingredients such as fillers and lubricants in order to assure good properties of the composition in the process of making final medicinal forms, particularly for compression into tablets. Suitable fillers are, e.g. calcium hydrogenphosphate, microcrystalline cellulose or lactose, suitable lubricants are magnesium stearate, precirol, sodium stearyl fumarate (Pruv) or talc.

The tablets of venlafaxine maleate according to the present invention may be produced by any standard tabletting technique, e.g. by wet granulation, dry granulation or direct compression. The tabletting methods that do not employ a solvent ("dry processes") are generally preferable.

In general, dry granulation procedures comprise mixing the solid excipients (except lubricants), compacting the mixture in a compactor (e.g. a roller compactor), or double compression, milling the compacted mass, screening the milled granules, mixing with a lubricant and compressing the mixture into tablets. Direct compression procedures generally comprise mixing the solid excipients in one or more stages and compressing the uniform mixture into tablets. After tablet formation, the tablets may optionally be coated.

The tablets can be of any size and shape. In one preferred embodiment the tablets are small or mini-tablets in size. Small tablets have a diameter of 3–6 mm while mini-tablets have a diameter of 1–3 mm. One or more of the tablets can be taken as such or, more preferably one or more are loaded into a single capsule to provide a unit dose. Most preferably, the small or mini-tablets provide additive amounts of the venlafaxine maleate without modifying the release profile. For example, by making a hydrogel round small tablet of diameter 5 to 6 mm and containing 37.5 mg of venlafaxine (as maleate), capsules containing 37.5 mg, 75 mg, and 150 mg of venlafaxine maleate can be formed by filling a standard No. 0 capsule with 1, 2, or 4 of the small tablets, respectively. Such an additive effect is not as easily obtained with a proportionally larger hydrogel tablet. This is because the release is a function of the volume to surface area ratio. Scaling up the amount and size of a satisfactory 37.5 mg tablet will likely not result in a satisfactory release profile for the resulting 150 mg tablet, for example, because the volume to surface area ratio is different between the two tablets. For each desired single dosage level, a separate formulation, size and/or shape would be needed. Similar proportionality issues arise with other delayed release tablet technologies. By using small tablets in a single capsule, only one tablet formulation and shape is needed to produce multiple dosage strengths. Typically a small or mini-tablet contains 5 to 50 mg of venlafaxine maleate, especially 10, 25, 30, 37.5, 40, and 50 mg. Depending on the size of the tablet and the capsule from 1 to 10 or more small or mini-tablets can be placed in the capsule.

In addition to filling capsules with small or mini-tablets, an extended release capsule can be formed by filling it with more traditional pellets, beads, and/or spheres. The pellets can be coated with an extended release coating or composition. In addition, different populations of coated pellets can be used in a single capsule, each providing a different release characteristic so that the aggregate release is sustained over a long period; i.e. 12 to 24 hours. Alternatively, the bead population can be substantially homogeneous. A preferred capsule of the pellet type is described in the above-mentioned U.S. Pat. No. 6,274,171 and related EP 0 797 991A1 wherein the venlafaxine hydrochloride used in these patents is replaced with the venlafaxine maleate compound of the present invention.

The venlafaxine maleate compound of the present invention can be used to treat any disease or condition that is treatable by venlafaxine. A venlafaxine-treatable disease or condition is one that could be improved by a serotonin or norepinephrine uptake inhibitor and specifically includes, without limitation, depressions, panic disorder, generalized anxiety disorder, obesity, post-traumatic stress disorder, late luteal phase dysphoric disorder, attention deficit disorders, Gilles de la Tourette syndrome, bulimia nervosa, and Shy Drager syndrome. See published U.S. patent application U.S. Ser. No. 2001/0012855 A1 for a description of the uses of venlafaxine and salts thereof. The venlafaxine maleate compound of the present invention can be used to treat such conditions by administering an effective amount to a patient in need thereof. An effective amount is generally known in the art and/or determined using routine skill. Typically the effective amount for a human is 30 to 300 mg of venlafaxine per day. The patients used herein include human and non-human mammals such as dogs, cats, and horses. The route of administration is not particularly limited and includes peroral, parenteral, and transdermal administration. Preferably, the venlafaxine maleate compound is administered orally via one or two unit dosage forms, especially extended release tablets or capsules, as described above.

The above description and details have been set forth with respect to venlafaxine maleate compounds, but also applies with equal force, mutatis mutandis, to all other low water-soluble venlafaxine salts. The entire disclosure in each of the patents mentioned in the above description is incorporated herein by reference. The invention will be further described with reference to the following non-limiting examples.

EXAMPLES

Example 1

Synthesis of Venlafaxine Hydrogenmaleate

In a 2-liter flask equipped with a mechanical stirrer, 250 g of venlafaxine base was dissolved under heating and stirring in 500 ml of acetone. Then 106.7 g of maleic acid was added to the hot clear solution and the resulting mixture

was heated until clear. The clear solution was allowed to cool to room temperature under stirring, and was kept at 4 C. for 30 minutes. The obtained crystals were isolated by filtration, washed with a small amount of acetone and dried overnight under reduced pressure at 40° C.

Yield: 332.3 g.
Identity confirmed by NMR.
No water present (K. Fischer titration)
M.p. 136–138° C., DSC peak at 137.78° C.
HPLC purity: min. 99.9%

Example 2

Round immediate release tablets, 6 mm in diameter, having a venlafaxine dosage strength of 37.5 were made by direct compression having the following ingredients and proportions.

Ingredients	mg/tablet
Venlafaxine hydrogenmaleate	53.125
Microcrystalline cellulose (Avicel PH 102)	29.875
Lactose monohydrate direct compression	16.00
Magnesium stearate	1.00

In SGF more than 70% of the venlafaxine was dissolved in 15 minutes.

Example 3

The following extended release hydrogel tablets were made by direct compression:

Ingredients	Ratio 1:1	Ratio 1:1.48
Venlafaxine hydrogenmaleate	53.125	53.125
HPMC (Methocel K 4M EP)	53.125	78.625
Microcrystalline cellulose (Avicel PH 102)	12.0	12.0
Dibasic calcium phosphate anhydrous (Emcompress)	5.0	5.0
Magnesium stearate	1.250	1.250

The invention having been described, it will be readily apparent to those skilled in the art that further changes and modifications in actual implementation of the concepts and embodiments described herein can easily be made or may be learned by practice of the invention, without departing from the spirit and scope of the invention as defined by the following claims.

We claim:

1. A venlafaxine maleate compound.

2. The venlafaxine maleate compound according to claim **1**, which is crystalline venlafaxine maleate.

3. The venlafaxine maleate compound according to claim **2**, which is crystalline venlafaxine hydrogenmaleate.

4. The venlafaxine maleate compound according to claim **3**, which is crystalline venlafaxine maleate anhydrate.

5. The venlafaxine maleate compound according to claim **1**, wherein said venlafaxine is pure or substantially pure (+) or (−) venlafaxine enantiomer.

6. A pharmaceutical composition comprising a venlafaxine maleate compound and a pharmaceutically acceptable excipient.

7. The pharmaceutical composition according to claim **6**, wherein said excipient is selected from the group consisting of calcium phosphates, microcrystalline cellulose, cellulose derivatives, polyvinylpyrrolidones, sugars, and combinations thereof.

8. The composition according to claim **6**, wherein said composition is a unit dosage form and said venlafaxine maleate is contained in an amount between 30 mg and 300 mg, calculated on venlafaxine free base.

9. The pharmaceutical composition according to claim **6**, wherein said composition is in the form of a tablet.

10. The pharmaceutical composition according to claim **9**, wherein said composition is an extended release composition.

11. The composition according to claim **10**, wherein said composition is a hydrogel tablet.

12. The composition according to claim **11**, wherein said composition is a once daily dose tablet.

13. The composition according to claim **9**, wherein said tablet comprises hydroxypropylmethyl cellulose and venlafaxine maleate.

14. The composition according to claim **12**, wherein said tablet comprises hydroxypropylmethyl cellulose and venlafaxine maleate.

15. The composition according to claim **12**, wherein said composition has a dissolution profile such that less than 30% of said venlafaxine maleate is released from said composition in 2 hours using either purified water or SGF at 37° C. with stirring at 100 r.p.m. in a basket apparatus.

16. The composition according to claim **15**, wherein said composition has a release profile that satisfies the following

Time (hours)	Average % venlafaxine maleate released
2	<30
4	30–55
8	55–80
12	65–90
24	>80

using USP Apparatus 1 (basket) at 100 rpm in purified water at 37° C.

17. The composition according to claim **6**, wherein said composition is in the form of pellets.

18. The composition according to claim **17**, wherein said composition is a once daily dose capsule.

19. The composition according to claim **17**, wherein said pellets have a dissolution profile that satisfies the following criteria:

Time (hours)	Average % venlafaxine maleate released
2	<30
4	30–55
8	55–80
12	65–90
24	>80

using USP Apparatus 1 (basket) at 100 rpm in purified water at 37° C.

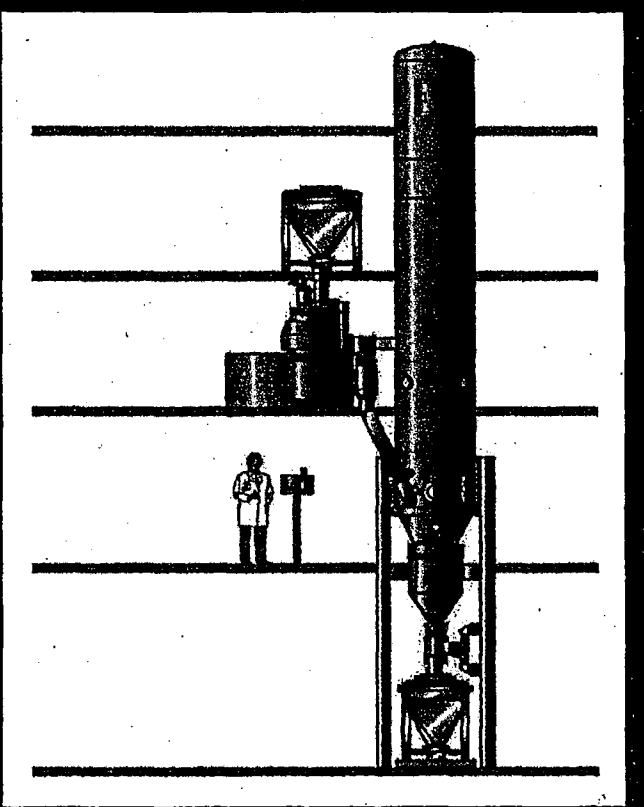
20. A method for treating a venlafaxine-treatable disease or condition, which comprise administering to a patient in need thereof an effective amount of a venlafaxine maleate compound.

EXHIBIT N

DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 154

Handbook of Pharmaceutical Granulation Technology

Second Edition



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11

Extrusion/Spheronization as a Granulation Technique

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1. INTRODUCTION

Extrusion/spheronization is a multiple step process capable of making uniformly sized spherical particles. The process is now being widely utilized in the pharmaceutical industry. This is the revision of the original chapter written by D. Erkoboni (1). As a pharmaceutical dosage form, pellets are defined as small, free flowing, spherical, or semispherical units made up of fine powders or granules of bulk drugs and excipients by variety of processes, extrusion and spheronization being one. It is primarily used as a method to produce multiparticulates for immediate and controlled release applications. The major advantage over other methods of producing drug-loaded spheres or pellets is the ability to incorporate high levels of actives without producing an excessively large particle. Mehta and Kislalioglu in their study demonstrated the incorporation of a poorly soluble drug in a pellet matrix up to 40% loading via extrusion/spheronization for controlled drug delivery (2).

Though the process is more efficient than other techniques for producing spheres, it is more labor and time intensive than the more common granulation techniques. Therefore, it should be considered as a granulating technique when the desired particle properties are essential and cannot be produced using more conventional techniques. However, more recently, pharmaceutical scientists worldwide have been able to use this method more easily due to advances in extrusion/spheronization equipment engineering, thus making it simple to use. Pellets offer scientists a great deal of development flexibility. Chemically incompatible ingredients, for instance, can be incorporated into single capsule using two pellet types each containing one of the incompatible ingredients. Pellets of different release characteristics can be combined to achieve the desired release pattern of the active ingredients. Pellets are characterized by a low surface area-to-volume ratio compared with powder or

granules, which provides excellent coating substrate. Typically, pellets range in diameter between 0.25 and 1.5 mm. Pellets are normally filled into hard gelatin capsules, or eventually compressed into tablets which disintegrate into individual pellets after oral intake.

Spheronization is a process invented by Nakahara in 1964. The patent describes a "Method and Apparatus for Making Spherical Granules" from wet powder mixtures (3). The equipment described in the patent was commercialized by Fuji Denki Kogyo Co. under the trade name Marumerizer®. The process went widely unnoticed in the pharmaceutical industry until 1970 when two articles were published by employees of Eli Lilly and Co. Conine and Hadley described the steps involved in the process including (a) dry blending, (b) wet granulation, (c) extrusion, (d) spheronization, (e) drying, and (f) screening (optional) (4). Reynolds went on to further describe the equipment and the mechanics of the process including the movement of the particles within the spheronizer (5). Both publications cite desirable product attributes that can be achieved, including good flow, low dusting, uniform size distribution, low friability, high hardness, ease of coating, and reproducible packing. Additionally, the resulting pellets offer not only technological advantages as mentioned before but also therapeutic advantages such as less irritation of the gastrointestinal tract and a lowered risk of side effects due to dose dumping and reproducibility of the drug blood levels (6). From the publication of these articles through present day the interest in extrusion/spheronization has continued to grow. The process has recently become established in industry but was primarily driven by academia in the interim. The increased popularity in recent years is, in part, due to a growing understanding of the effects of process parameters and material characteristics.

In recent times, hot-melt extrusion (HME) has gained subsequent industry and academic attention and is in the phase of further process maturity for ultimately gaining wide spread popularity. HME is somewhat widespread in the plastics industry for the production tubes, pipes, wires, and films. For pharmaceutical systems, this method has been used to prepare granules, sustained release tablets, and transdermal drug delivery systems (7). The advantage of HME is that it does not require the use of solvents and water and few processing steps are needed making the process somewhat simpler, efficient, and continuous. The disadvantage of HME is that it may use complicated know-how and typically employs high temperatures around and over 100°C as a processing requirement. However, it has been used as a method to increase the solubility of a poorly soluble drug, to taste mask a bitter drug and overall for controlled release dosage form purposes. The bioavailability of the drug substance has been demonstrated to improve when it is dispersed at the molecular level in hot-melt extruded dosage forms. Several examples of melt-extruded molecular dispersions were presented by Breitenbach and Mägerlein (8).

A recent patent (9) describes melt- extrusion process as being used to produce improved controlled release characteristics. The authors described the process which includes mixing together a therapeutically effective agent, a water-insoluble retardant, and a binder to form a homogeneous mixture, heating the mixture and thereafter extruding the mixture into strands. The strands are then cooled, reduced to the desired sizes.

The number of hot-melt extrusion patents issued for pharmaceutical systems has increased more than sixfold annually since the early 1980s, with the United States, Germany, and Japan leading the field. The field of melt extrusion technology is growing very rapidly and its use to produce films for transmucosal and transdermal drug delivery applications was presented by McGinity and Repka (10).

2. APPLICATIONS

Potential applications are many including both immediate and controlled release. In a paper by Sood et al., extrusion/spheronization method was used to develop controlled release dosage forms for diltiazem hydrochloride (11). Two or more actives can easily be combined in any ratio in the same unit. These combination products can contain actives that are incompatible or have varying release profiles. Spheres can be used as a method to limit drug migration. Physical characteristics of the active ingredients and excipients can be modified to improve physical properties and downstream processing. As an example, a low-density, finely divided active can be pelletized to increase density, improve flow, and limit dusting (12). Mehta et al. showed that this technique can be used for the development of zero order controlled release drug delivery of poorly soluble drugs (13). Functional coatings can be applied easily and effectively. Dense multiparticulates disperse evenly within the gastrointestinal tract and can be used to prolong gastrointestinal transit times (14,15) or to improve tolerance of some compounds. Regardless of the application, care must be taken to achieve the required sphere or granule properties.

Spheres for controlled release coating applications will likely have significantly different physical requirements than granules for compression. A product to be coated for controlled release should have a uniform size distribution, good sphericity and surface characteristics as well as low friability. Once coated, the sphere should have the desired release characteristics. Additionally, if the coated spheres are to be compressed into tablets, they will require sufficient strength to withstand the forces of compression. Upon disintegration of the tablet, the individual spheres must retain their original release profile. Physical properties such as flow, density, friability, porosity, and surface area become important for granules intended for compression into tablets. The granules should have good deformation and bonding characteristics to form tablets having desirable physical properties. Drug release from the final dosage form must meet the target specification.

Product produced using extrusion/spheronization can range from barely shaped, irregular particles with physical properties similar to a conventional granule to very spherical particles having properties that are drastically different (16). Tableting characteristics can be modified by altering the composition of the spherical particles (17), granulating fluid (18), or the process conditions used to produce them (19). Compaction studies conducted on spheres similar to those used for controlled release applications show the bonding and densification that occur during extrusion/spheronization can alter the deformation characteristics of some materials (18). Microcrystalline cellulose (MCC), which deforms plastically in the dry powder state, exhibits elastic deformation followed by brittle fracture once spheronized (17). The deformation characteristics, coupled with the larger size particles result in reduced bonding sites and the production of weak compacts. A compaction profile of MCC and spheres prepared from MCC is shown in Figure 1.

The point is not to dwell on the properties required for each application, but rather to reinforce the fact that each application will have very specific requirements. One must first understand the properties required and then tailor the process to yield the desired effects. The effects of process and formulation variables will be discussed next.

A review of the literature shows that most investigators have tried to understand small components of this process isolated from other effects. They have focused on particular formulation or process parameters. It is valuable to have

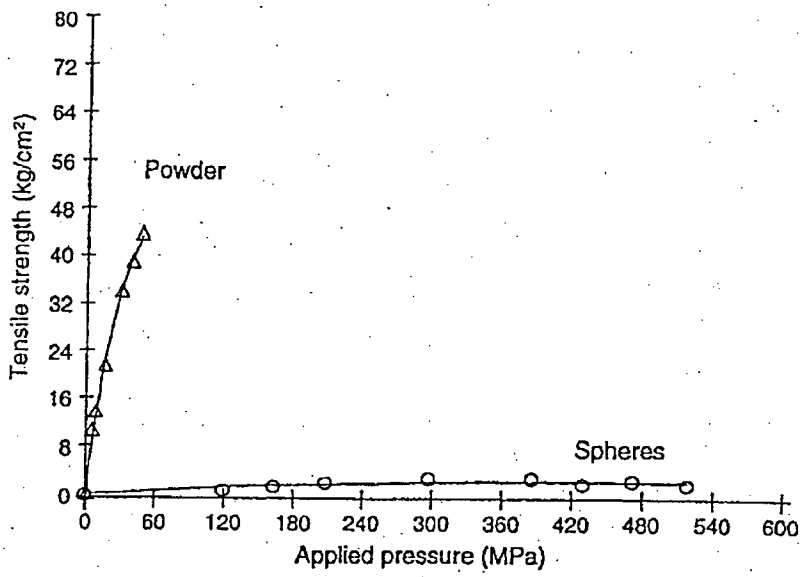


Figure 1 Compaction profiles of microcrystalline cellulose powder and spheres. (From Ref. 17.)

a detailed understanding of the main variables; however, this approach fails to take into consideration the high degree of interaction that exists between the variables. The use of statistical experimental design is a valuable tool to understand not only the main effects but also the interactions that can have a profound effect on the characteristics of the resulting particles (20–22). Additionally, these techniques are extremely useful during product/process development to understand the effect of variables and control them to produce product having desired attributes (23). After pointing out the benefits of design methodology in this application, it should be understood that, for simplicity, much of the discussion to follow will address the various topics individually. In reality, however, they truly cannot be isolated from one another. This chapter will review and discuss the general process, equipment types, and the effect of process and formulation variables on the properties of spherical granules.

3. GENERAL PROCESS DESCRIPTION

Extrusion/spheronization is a process requiring at least five units of operation with an optional sixth screening step. First, the materials are dry mixed (i) to achieve a homogeneous powder dispersion and then wet granulated (ii) to produce a sufficiently plastic wet mass. The wet mass is extruded (iii) to form rod-shaped particles of uniform diameter that are charged into a spheronizer and rounded off (iv) into spherical particles. The spherical particles are then dried (v) to achieve the desired moisture content and optionally screened (vi) to achieve a targeted size distribution. The process flow diagram, shown in Figure 2, has been used to show each of the process steps along with critical variables associated with them (24). The end product from each of the steps is shown in Figure 3.

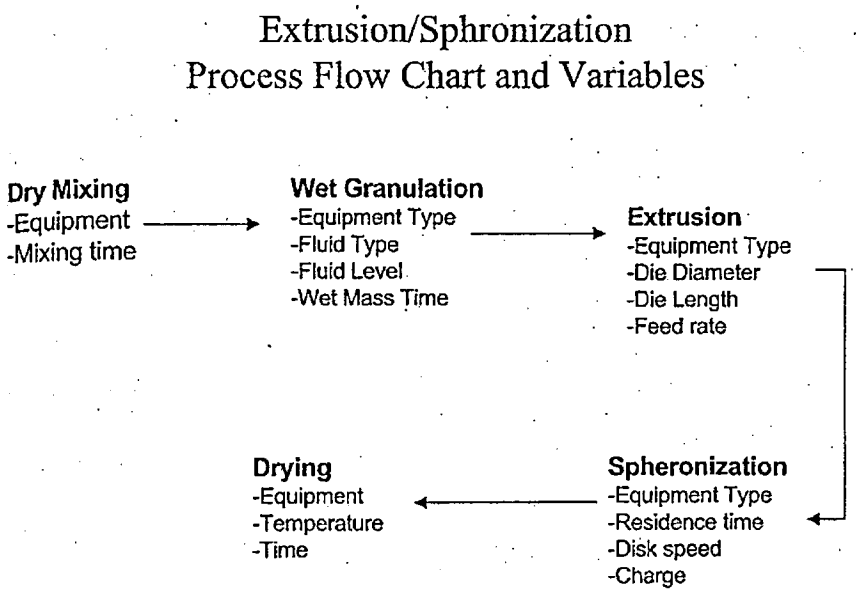


Figure 2 Process flow chart of the extrusion/spheronization process showing the process variables for each individual step. (From Ref. 24.)

4. EQUIPMENT DESCRIPTION AND PROCESS PARAMETERS

4.1. Dry Mixing

During the first step, powders are dry mixed to achieve a uniform dispersion prior to wet granulation. It is generally carried out in the same mixer used for the granulation;

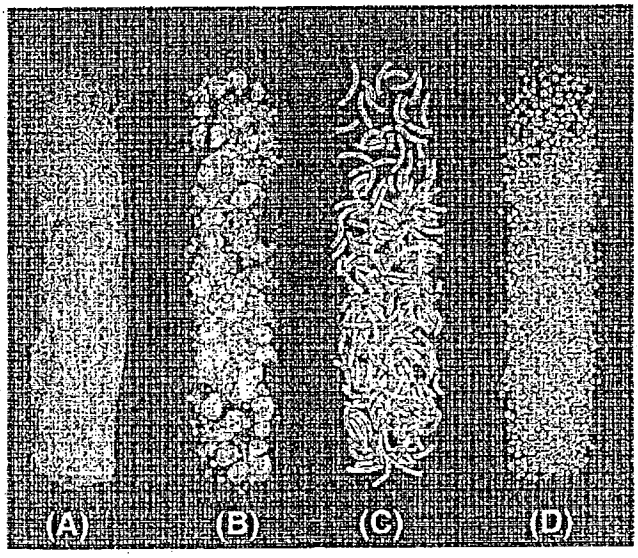


Figure 3 Product produced by the first four extrusion/spheronization process steps. (A) Powder from dry mixing; (B) granules from granulation; (C) extrudate from extrusion; and (D) spheres from spheronization.

however, if a continuous granulator is used, a separate mixer is required for the dry mix. This step is typically taken for granted because wet massing follows. The uniformity of the dry mix, however, can have a significant effect on the quality of the granulation and, in turn, the spherical particles produced. An uneven distribution of materials having wide differences in properties such as size and solubility can result in localized over wetting, at least initially, during the granulation step. The more soluble and finely divided components can also dissolve and become part of the granulating fluid. The fluids, rich in soluble compounds, can either remain as overwet regions or, with continued wet massing, can be redistributed (25). Sphere uniformity (size and shape) is very much dependent on the uniform distribution and composition of the granulating fluid which include not only the solvent but also any dissolved ingredients.

4.2. Granulation

The second step is granulation, during which a wet mass having the requisite plasticity or deformation characteristics is prepared. With a few exceptions, this step is similar to conventional granulation techniques used to produce product for compression. It is typically carried out in a batch type mixer/granulator; however, any equipment capable of producing a wet mass, including the continuous type, can be used. Batch type processors include planetary mixers, vertical or horizontal high shear mixers, and sigma blade mixers. Examples of continuous mixers include the Nica M6 instant mixer (26) and high shear twin screw mixer/extruders (27). The high shear twin screw mixer/extruders have mixer/feeders that are capable of shearing and kneading the feed materials. Dry powders and fluids are fed in through separate ports and mixed by the action of the extruder blades and screws. The mixer/extruder is capable of being configured to customize the amount of shear and energy used in the process by changing the configuration of the mixing blades. This can have an impact on the properties of the extrudate produced (28). As with the batch processors it is critical to achieve a uniform level of fluid within the wet mass. The proper fluid/solids ratio is accomplished by maintaining a steady powder and fluid feed into the mixer/extruder. Both are critical; however, the powder feed is the most problematic. Small variations in feed rates can cause significant shifts in the moisture content of the granulation and, therefore, the quality of the spherical particles produced.

The two major differences in the granulation step, as compared to typical granulations for compression are the amount of granulating fluid required and the importance of achieving a uniform dispersion of the fluid. The amount of fluid needed to achieve spheres of uniform size and sphericity is likely to be greater than that for a similar granulation intended for tableting. Instruments such as a ram extruder (29) and a torque rheometer (30) have been used to characterize the flow characteristics of granulations for use in extrusion/spheronization. They are useful tools in quantifying the rheological effect of formulation and process variations in the granulation. The ram extruder has been used to characterize the flow of wet masses through a die, which has been divided into stages. They are: (a) compression, where the materials are consolidated under slight pressure, (b) steady-state flow, where the pressure required to maintain flow is constant, and (c) forced flow, where an increase in force is required to maintain flow. The three stages are shown in the force vs. displacement profile in Figure 4.

The change from steady state to forced flow is caused by the movement of fluid under pressure. Extrusion in a ram extruder is continuous, and this phenomenon is

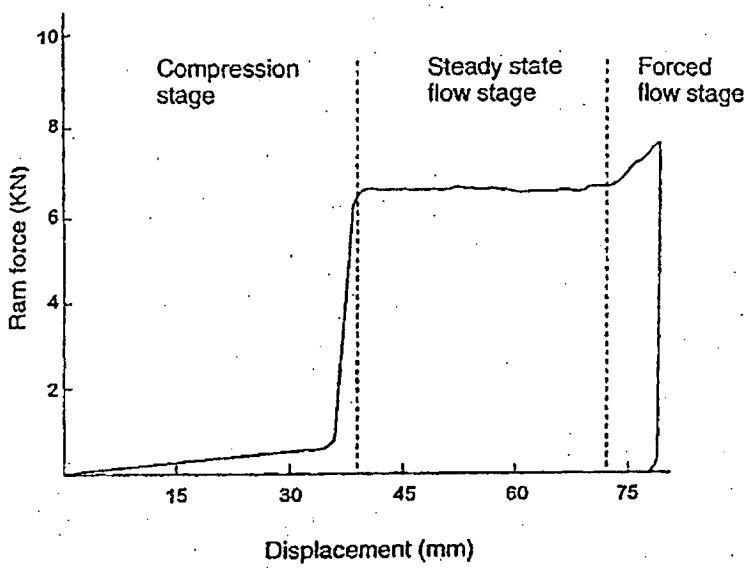


Figure 4 A force–displacement profile for a microcrystalline cellulose–lactose–water mixture showing the three stages of extrusion on a ram extruder: Compression, steady-state flow, and forced flow (ram speed, 4 mm/sec; die diameter, 1.5 mm; L/R ratio, 12). (From Ref. 31.)

less likely to be seen in extruders that are discontinuous such as gravity-feed models (32). A diagram of a ram extruder is shown in Figure 5.

Regardless of the mixer used, one must remember that the downstream process steps of extrusion and spheronization are very dependent on the level of water contained in the granulation and the quality of its dispersion. High-energy mixers such as high shear mixers and high shear twin screw mixer/extruders can cause a significant rise in temperature. It may be necessary to use a jacket to guard against heat build-up. High temperatures can result in a greater than tolerable level of evaporation (33) or an increase in the solubility of some of the solids. A reduction in fluid will reduce the plasticity of the granulation, while an increase in solubility will increase the weight ratio of granulating fluid since the solute is then part of that fluid (34). The water solubility of the drug in the granulation plays a key role in determining granulation end point for extrusion/spheronization process. A highly water soluble drug will dissolve in the granulation whereas a highly insoluble drug will have wetting problems during the granulation step. Upon extrusion and during spheronization step a granulation containing a highly insoluble drug at a high dose will have a higher tendency to release moisture due to which the moisture will migrate to the surface of the extrudates, which might cause interpellet sticking. In order to avoid this Mehta et al. in their work demonstrated the use of small quantities of talc to adsorb the surface moisture which helped in the spheronization step without altering the drug release from the resulting pellets (2).

4.3. Extrusion

The third step is the extrusion step which forms the wet mass into rod-shaped particles. The wet mass is forced through dies and shaped into small cylindrical particles having a uniform diameter. The extrudate particles break at similar lengths under

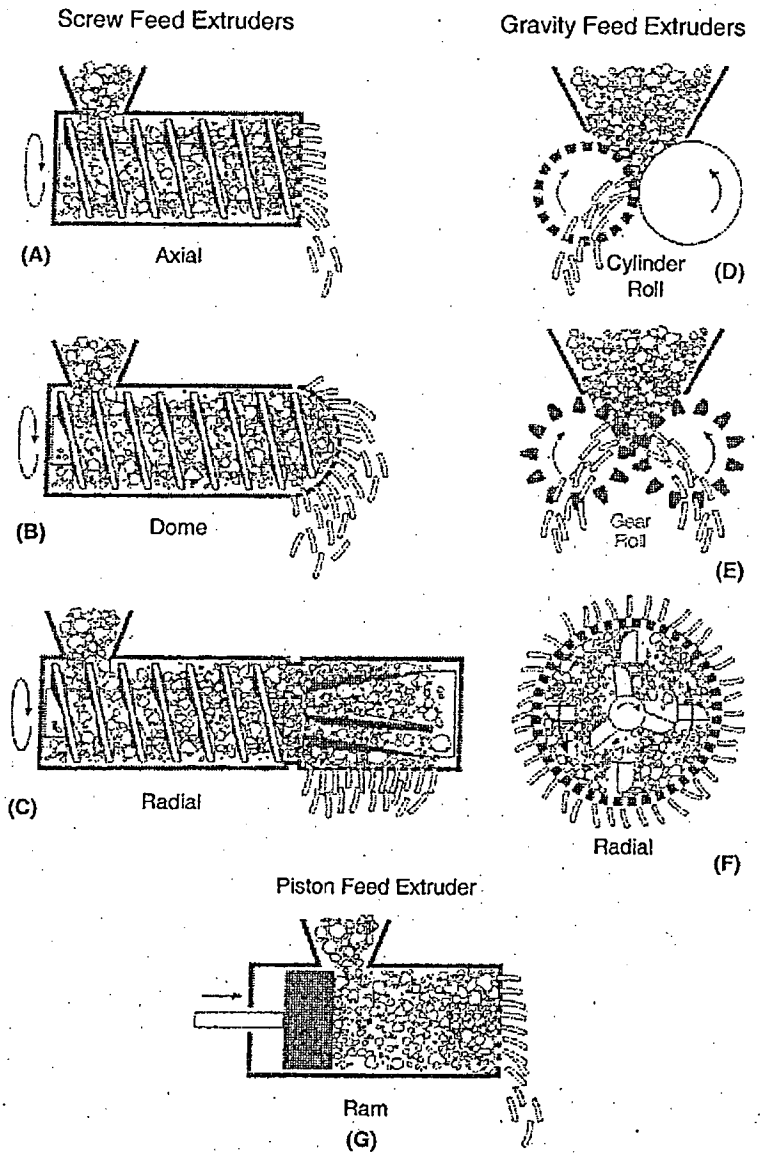


Figure 5 Schematic diagrams of extruder types used in extrusion/spheronization.

their own weight. The extrudate must have enough plasticity to deform but not so much to adhere to other particles when collected or rolled in the spheronizer.

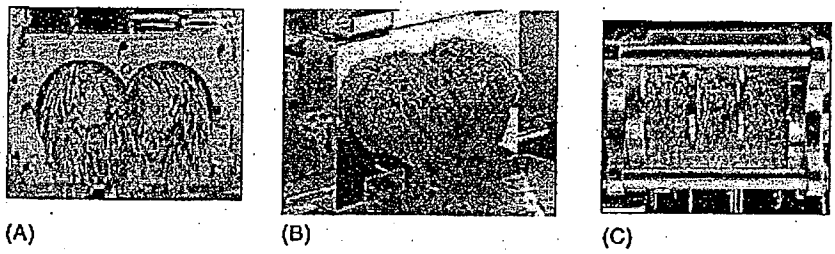
Extruders come in many varieties but can generally be divided into three classes based on their feed mechanism. They include those that rely on a screw, gravity or a piston to feed the wet mass into the extrusion zone (35). Examples of extruders from each class are shown in Figure 5. Screw feed extruders include the (a) axial or end plate, (b) dome, and (c) radial type, while gravity-feed extruders include (d) cylinder, (e) gear, and (f) radial types. The screw and gravity-feed types are used for development and manufacturing with the radial varieties being the most popular for pharmaceutical applications. The piston feed or ram extruder is primarily used in research as an analytical tool.

Screw extruders have either one (single) or two (twin) augers that transport the wet mass from the feed area to the extrusion zone. During the transport process, the screws compress the wet mass removing most of the entrapped air. Studies have been conducted on the ram extruder to understand this compression or consolidation stage. They have shown the apparent density of the wet mass plug prior to extrusion is approximately equal to the theoretical apparent particle density, indicating that nearly all of the voids were eliminated (31). Twin screw extruders generally have a higher throughput than single screw models, while single screw extruders compress and increase the density of the extrudate more. Other features that can affect the density of the extrudate are the spacing of the turnings on the screw and the space between the end of the screw and the beginning of the die (36). Turnings that are wide and regularly spaced minimize the amount of compression during material transport. Screws with closer or progressively closer spacing between the turnings will result in more compression and produce a denser extrudate. Space between the screw and the die results in a void into which material is deposited and compressed. The greater the space, the more compression takes place prior to extrusion. As material builds up, pressure increases and causes the material to be forced, under hydraulic pressure, to flow through the die. When space between the screw and the die is at a minimum, extrusion takes place as material is compressed in the nip, between the extruder blade and the die.

The primary difference between the various types of screw extruders is in the extrusion zone. An axial or dome extruder transports and extrudes the wet mass in the same plane. Axial extruders force the wet mass through a flat, perforated end plate, typically prepared by drilling holes in a plate. The thickness of the plate can be more than four times the hole diameter, resulting in high die length to radius (L/R) ratios. An axial extruder is shown in Figure 6(A).

Dome extruders use a dome or half sphere shaped screen as the die. It is prepared by stamping holes in metal stock having a similar thickness as the hole diameter. This results in a die L/R ratio close to 2, however, variations in screen thickness are possible resulting in a slightly higher or lower ratio. A dome extruder is shown in Figure 6(B).

Unlike axial and dome extruders, radial extruders extrude the wet mass perpendicular to the plane of transport. Material is transported to the extrusion zone where it is wiped against the screen die by an extrusion blade. The mass is forced through the die by pressure generated at the nip. A screw feed radial extruder is shown in Figure 6(C).



(A) (B) (C)

Figure 6 Types of extruders. (A) Axial; (B) dome and (C) radial. (Courtesy of the LCI Corporation.)

As with dome type extruders the die is a stamped screen. Due to the shorter die lengths and the increase number of holes or dies, dome and radial extruders have the advantage of higher throughput as compared to the axial type.

As with almost every step in extrusion/spheronization, heat build-up during extrusion is a significant concern. This is especially true of the screw fed extruders. Axial extruders generate heat due to their long die lengths. Radial extruders can have a significant heat differential over the width of the screen. Materials fed into the extrusion zone will have the lowest temperature. However, as material moves to the front of the zone, the temperature increases due to the longer residence time of material. Of the screw feed extruders, the dome type has the highest rates and is least likely to generate significant heat over an extended period.

Gravity-feed extruders include a cylinder, gear, and radial type. The cylinder and gear both belong to a broader class referred to as roll extruders. Both use two rollers to exert force on the wet mass and form an extrudate. The cylinder extruder has rollers in the form of cylinders, one solid and one hollow with drilled holes to form the dies. The wet mass is fed by gravity into the nip area between the two cylinders and forced through the dies into the hollow of the cylinder. Gear type extruders have rollers in the form of hollow gears. The dies are holes drilled at the base of each tooth. Wet mass is forced through the holes and collected in the hollow of the gears as the teeth and the base areas mesh. The last type of gravity-feed extruder to be discussed is the radial type. One or more arms rotate to stir the wet mass as it is fed by gravity. Rotating blades wipe the wet mass against the screen, creating localized forces sufficient to extrude at the nip. There is no compression prior to extrusion which is the major difference between the gravity and screw feed radial extruders. A gravity-feed extruder is shown in Figure 7.

The primary extrusion process variables are the feed rate, die opening, and die length. The water content of the granulation is also very critical, since the properties of the extrudate and resulting spheres are very dependent on the plasticity and cohesiveness of the wet mass. The process variables and water content have been the focus of many studies. Harrison, Newton, and Rowe studied the flow of the wet mass as it is forced through a die (29,31,37,38). They determined that steady-state flow (described earlier and shown in Fig. 4) was essential to produce a smooth extrudate, which results in uniformly sized spherical particles having good sphericity and surface characteristics. Materials and processes that did not result in steady state, a condition referred to as forced flow, produced extrudate having surface impairments. In moderate cases, the surface is rough, while in more severe cases, a phenomenon commonly referred to as shark-skinning occurs. Examples of smooth extrudate and shark-skinned extrudate are shown in Figure 8(A) and (B), respectively.

Force–displacement profiles of microcrystalline cellulose (MCC) and water at various ratios, MCC, lactose, and water at a 5:5:6 ratio, and lactose and water at a 8:2 ratio, developed by Harrison et al., are shown in Figure 9.

Steady state was possible with the MCC and MCC:lactose samples but not with lactose alone. As can be seen with the MCC samples, the duration of the compression stage was water level dependent with no effect seen on the steady state stage. Additional studies indicated the effect of ram speed (extrusion speed) and die L/R ratio. An increase in ram speed increased duration of the steady-state stage with no effect on the compression stage. The L/R ratio had no effect on either compression or steady state. Wet mass composition, therefore, influenced the ability to achieve steady state while the water level and ram speed influenced duration. Higher water levels decreased the force to produce steady-state flow but increased

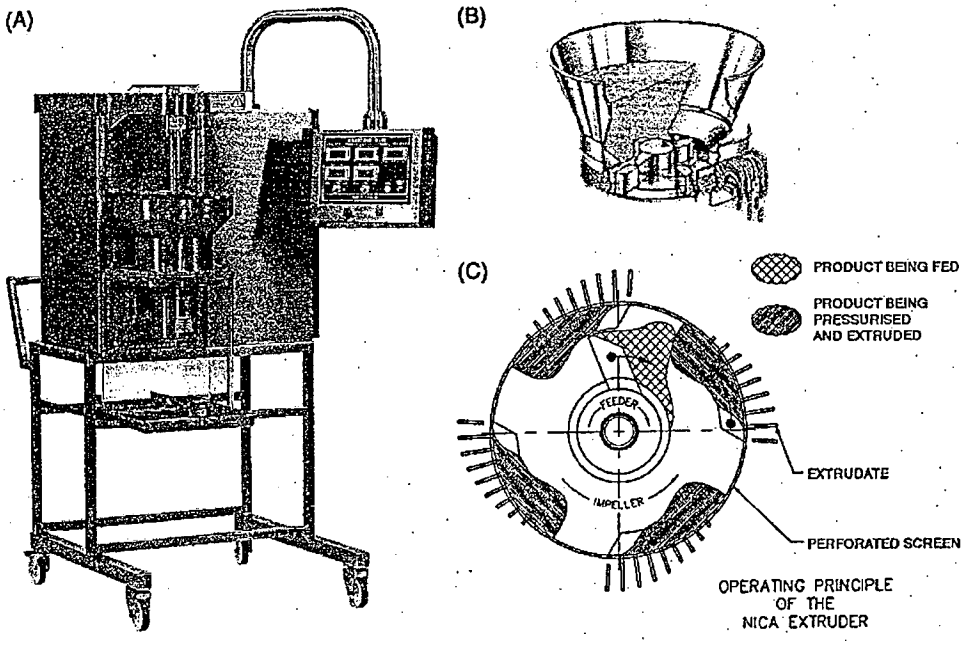


Figure 7 (A) Gravity-feed rotary extruder; (B) close-up showing the extrusion zone; (C) operating principle of gravity-feed extruder. (Courtesy of Niro Pharma Systems.)

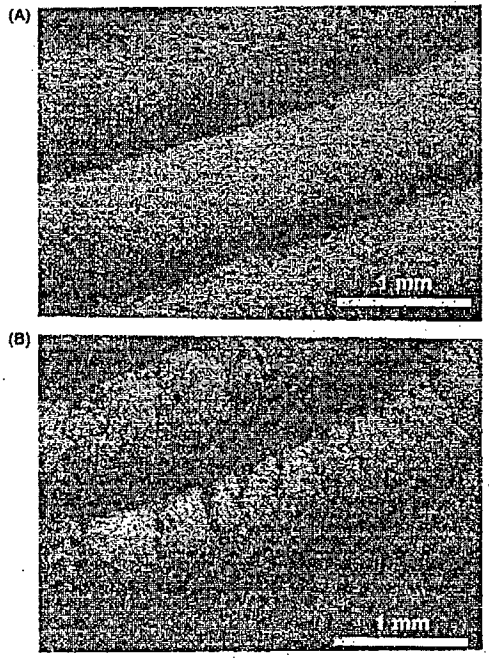


Figure 8 Scanning electron micrographs showing an example of (A) smooth extrudate and (B) extrudate having surface impairment, or shark-skinning.

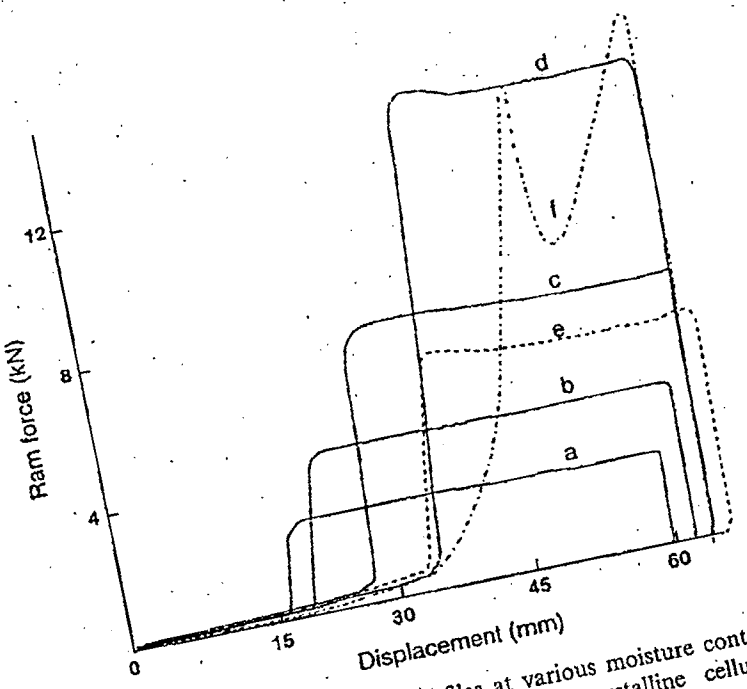


Figure 9 Force–displacement profiles at various moisture contents of mixtures of microcrystalline cellulose and water: (a–d) microcrystalline cellulose–lactose–water (5:5:6); (e) lactose–water (8:2); (f) at a ram speed of 4 mm/sec, die diameter of 1.0, and a L/R ratio of 12. Percentage of moisture content of microcrystalline cellulose–water mixture: a, 59.4; b, 51.1; d, 45.0. (From Ref. 29.)

the duration. Faster ram speeds (extrusion rates) increased the duration of steady state and increased the force. As discussed in the following text, other investigators have reported the correlation between extrusion force and sphere quality.

Fechner et al. indicated that for an optimum extrusion process, a mixture of spongelike and gel-like behavior might be desirable which are possible by the use of MCC and powder cellulose (39).

Harrison et al. also indicated that a uniform lubricating layer at the die wall interface must occur to eliminate the slip-stick phenomenon responsible for forced flow. Development of a lubricating layer was dependent on the length of the die (a minimum length required), wall shear stress and upstream pressure loss. They represent the frictional forces at the die wall interface and the estimated pressure loss at zero die length in the barrel of the ram extruder. The method for deriving these values is described in Ref. 27. These parameters allow for a quantitative comparison between formulations and process; however, no specific values can be targeted since they vary with materials.

Pinto et al. also showed that, at slow ram speeds, water moves toward the die wall interface and acts as a lubricant resulting in reduced extrusion forces. At higher speeds water is unable to move rapidly through the mass resulting in higher forces (40). They indicated that the water content and its distribution are critical in determining the particle size and sphericity of the product. Lower water content and higher speed will reduce the size and sphericity of the particles. The extrusion speed and water content should be adjusted to achieve the desired effect. Other researchers have investigated the effect of die length using gravity-feed radial extruder. Hellén et al. indicated the extrudate became smoother and more bound as the L/R ratio

of the die was increased (41). Vervaet et al. reported that a higher L/R ratio enables the use of lower water levels to achieve a more bound extrudate (42). This also increased the range (drug loading and water level) over which quality spheres could be produced. They attributed the increased latitude and capability to increased densification and resulting well-bound extrudate. The average pore diameter and bulk density reported for extrudate prepared from various MCC:DCP:water ratios at two L/R ratios are shown in Table 1.

Baert et al. also indicated a similar increase in latitude when a cylinder extruder having an L/R ratio of 4 was compared to a twin screw extruder having a L/R ratio of close to 1.8 (43). Other studies have shown that there is an optimal pressure range over which extrudate capable of yielding acceptable spheres can be produced. Shah et al. demonstrated the correlation between screen pressure yield and density (44). A high yield of spheres within a targeted narrow size distribution was produced as long as the screen pressure was maintained within a given range. The relationship between yield and screen pressure is shown in Figure 10.

While many of the researchers have indicated a need for a more cohesive extrudate, few have expressed a need to remove all surface impairments. Some researchers have indicated that spheres having acceptable characteristic can be produced from extrudate having shark-skinning. O'Connor and Schwartz have found the presence of shark-skinning to be advantageous in facilitating the breakage of the extrudate during the spheronization step (45).

Experimental design studies conducted to concurrently investigate the effect of extrusion as well as other process and formulation variables have indicated the extrusion variables to be less significant than granulating fluid level or variables of the spheronization step. Hasznos et al. determined that extruder speed had little effect on the size distribution of the final product or moisture change during processing as compared to the spheronization variables (46). Hilemann et al. indicated that, when water/MCC ratios are held constant, a change in screen size results in a significant change in the size distribution (47). However, in a study where water level was included as a variable, Erkoboni et al. have shown that the effect of screen size on size distribution is small compared to the effect of a change in water level. A change in water level can shift the mean size and still result in an acceptable distribution (21). This is in agreement with earlier work by Malinowski and Smith who also showed the mean particle size is typically smaller than the size of the screen itself due to shrinking during the drying step (12). Vervaet et al. have presented an excellent review of extrusion spheronization (48).

Table 1 Average Pore Diameter and Bulk Density of Extrudate Composed of DCP–Avicel PH-101–Water Mixture, Extrudated Using Screens with Different L/R Ratios

Composition DCP–Avicel–water (w/w)	L/R ratio of screen	Average pore diameter (μm)	Bulk density (g/mL)
150:380:470	4	0.982	1.132
150:400:450	4	0.992	1.211
150:380:470	2	1.249	0.949
150:400:4502	2	1.292	0.947

Source: From Ref. 42.

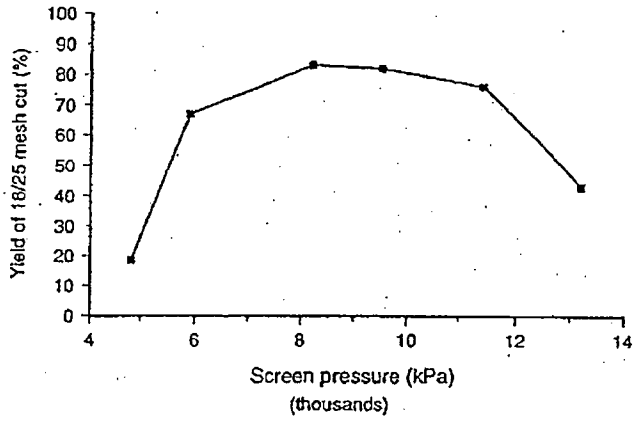


Figure 10 The effect of extruder screen pressure on the yield of particles within an acceptable distribution. (From Ref. 44.)

4.4. Spheronization

The fourth step in the extrusion/spheronization process is the spheronization step. It is carried out in a relatively simple piece of equipment. The working parts consist of a bowl having fixed sidewalls with a rapidly rotating bottom plate or disk. The rounding of the extrudate into spheres is dependent on frictional forces. The forces are generated by particle-to-particle and particle-to-equipment interactions. For this reason the disk is generally machined to have a grooved surface which increases the forces generated as particles move across its surface. Disks having two geometric patterns are produced, a cross-hatched pattern with the grooves running at right angles to one another and a radial pattern with the grooves running radially from the center. The two varieties are shown graphically in Figure 11.

Some studies have shown the rate of spheronization to be faster with the radial pattern; however, both plates will result in acceptable product (35).

During the spheronization step, the extrudate is transformed from rod-shaped pellets into spherical particles. This transition occurs in various stages. Once charged

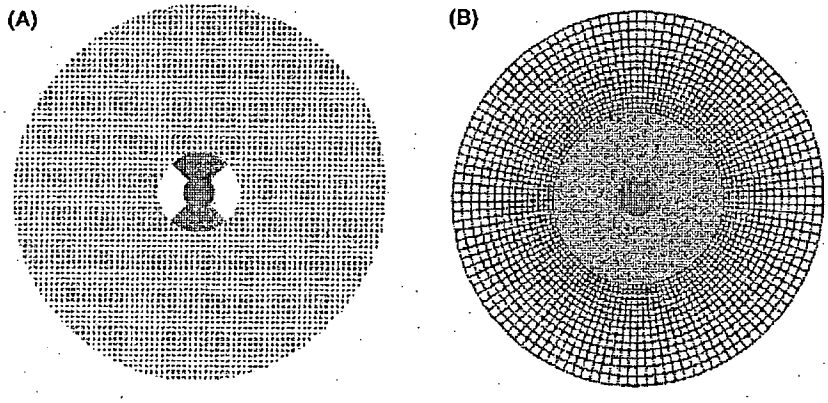


Figure 11 Spheronizer disks having two geometric patterns: (A) a cross-hatched pattern with the groves running at right angle to one another and (B) a radial pattern with the groves running radially from the center.

into the spheronizer, the extrudate is drawn to the walls of the extruder due to centrifugal forces. From here what happens is very much dependent on the properties of the extrudate. Under ideal conditions, the extrudate breaks into smaller, more uniform pieces. Within a short period of time, the length of each piece is approximately equal to the diameter, due to attrition and rapid movement of the bottom plate or disk. The differential in particle velocity as they move outward to the walls, begin to climb the walls and fall back onto the rotating bed, along with the angular motion of the disk results in a rope-like formation (5). Figure 12 shows the rope-like formation of the extrudates.

This formation can be a critical indicator of the quality of the granulation or extrudate. As pointed out by Reynolds (5), the disk rotating without movement of the product indicates an over wet condition. The condition is caused either from a granulation that was initially over wet or migration of water or a fluid ingredient to the surface of the extrudate during extrusion or spheronization.

As mentioned, the transformation from cylinder-shaped extrudate to a sphere occurs in various stages. Two models have been proposed to describe the mechanism and are shown graphically in Figure 13.

The model proposed by Rowe in 1985 describes a transition whereby the cylindrical particles (Fig. 13-2A) are first rounded off into cylindrical particles with rounded edges (Fig. 13-2B), then form dumbbell-shaped particles (Fig. 13-2C), ellipsoids (Fig. 13-2D), and finally spheres (Fig. 13-2E) (35). The second model proposed by Baert et al. in 1993 suggests that the initial cylindrical particles (Fig. 13-1A) are deformed into a bent rope-shaped particle (Fig. 13-1B), then form a dumbbell with a twisted middle (Fig. 13-1C). The twisting action eventually causes the dumbbell to break into two spherical particles with a flat side having a hollow cavity (Fig. 13-1D). Continued action in the spheronizer causes the particles to round off into spheres (Fig. 13-1E). When the sphere is fractured a hollow particle is revealed (49). The exact mechanism is likely to be composition dependent. If the extrudate is overwet, particle growth will occur resulting in a broad size distribution. Under wet extrudate will not have enough plasticity to further round off in the spheronizer; the result is the formation of dumbbells. The scanning electron micrographs in Figure 14 show an example of good spheres produced from a sufficiently plastic mass and dumbbells that would not deform further.

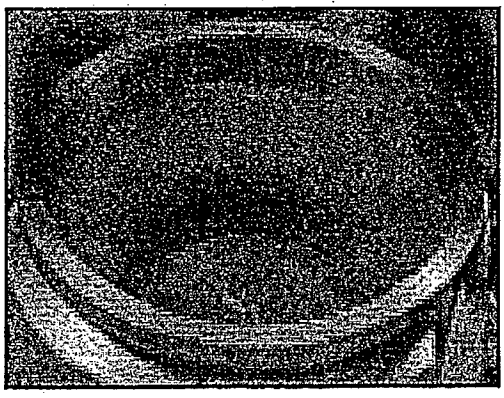


Figure 12 A characteristic rope-like formation in a spheronizer bowl during operation.

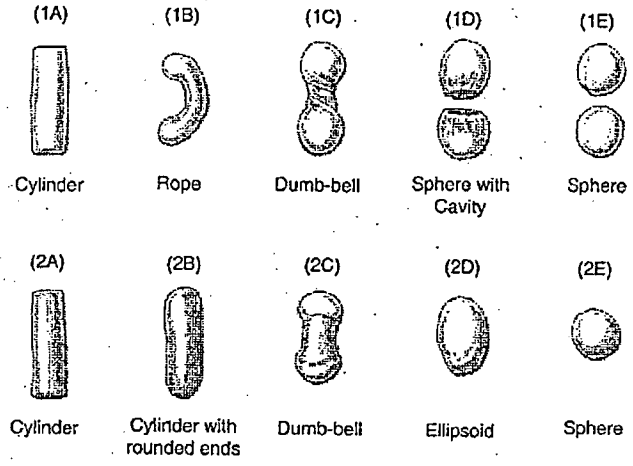


Figure 13 A graphic representation of the two models proposed to describe the mechanism of spheronization. The model proposed by Baert et al. (38) describes a transition from initial cylindrical particles (1A) into a bent rope (1B), dumbbell (1C), two spherical particles with a hollow cavity (1D), and spheres (1E).The model proposed by Rowe (25) describes a transition from cylindrical particles (2A) into cylindrical particles with rounded edges (2B), dumbbells (2C), ellipsoids (2D), and spheres (2E). (From Refs. 35,49.)

Of the two process steps unique to extrusion/spheronization, the first, extrusion, is a continuous process while the second, spheronization, is a batch process. To make the process viable for commercial operations, two systems have been developed to enable the extruder to continuously feed material to the spheronizer(s). The

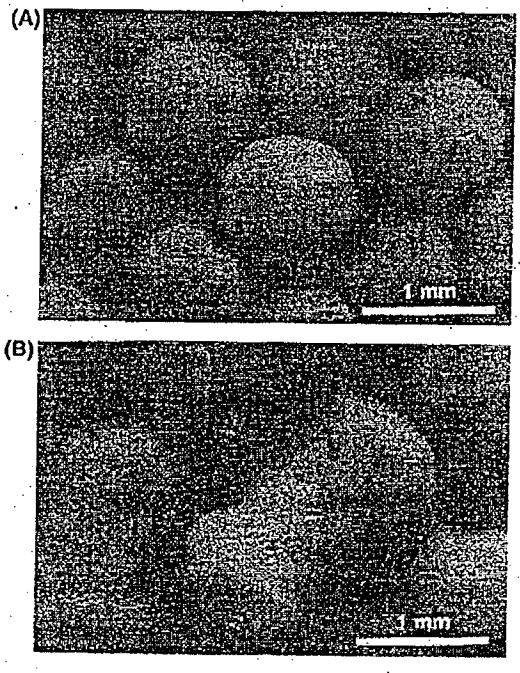


Figure 14 An example of (A) good spheres produced from a sufficiently plastic mass and (B) dumbbells that would not deform further produced from underwet extrudate.

first system is a semicontinuous shuttle system and the second is a cascade system. The shuttle system is typically used when uniform particles are required, such as for controlled release coating applications. The cascade system, however, can be used for applications where less size and shape uniformity is required, such as granulations intended for compression.

The shuttle system uses two spheronizers in parallel. It is designed to fill one spheronizer while the second is in the middle of its cycle, continue to collect extrudate in a shuttle receptacle while they are both full and operational, and fill the second after it empties and the first unit is in the middle of its cycle. The shuttle system operation is shown graphically in Figure 15.

A picture of a spheronizing system having twin spheronizers is also shown in Figure 16.

The cascade operation uses one or more spheronizers that are modified to have the disks some distance below the discharge chute (36). This results in a spheronization zone having a fixed volume. The product is continually fed from either the extruder or a previous spheronizer. As the charge volume grows from incoming material some product is discharged. The residence time is dictated by the feed rate. The reduced size and shape distributions are due to the percentage of material that does not reside in the spheronization zone for the intended period of time. The number of spheronizers placed in sequence depends on the desired outcome. However, if only a slight rounding with minimal densification is required, one spheronizer with a short residence time will be sufficient.

A commercial manufacturing of pellets using the extrusion/spheronization process can be accomplished by discharging the formed pellets from the spheronizer in a continuous fluid bed unit. This provides the semiautomatic commercial setup. Figure 17 illustrates a typical setup in such an equipment configuration.

Variables in the spheronization step include spheronizer size, charge, disk speed, and residence time. A number of studies have shown each of the variables

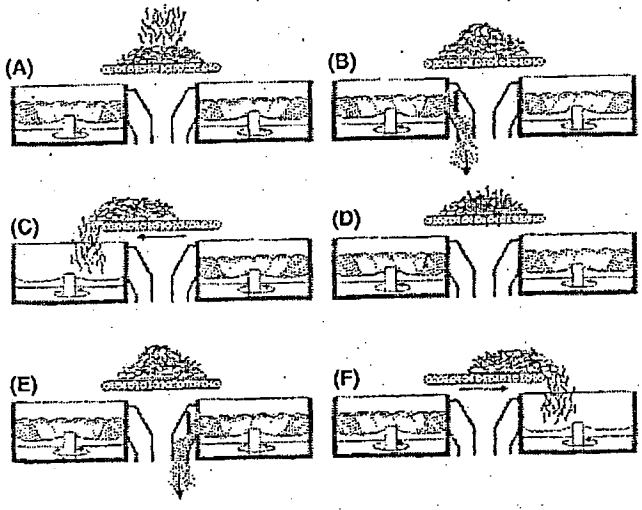


Figure 15 A graphic representation of twin spheronizer shuttle system using two spheronizers in parallel and shuttle receptacle. (A) When both units are full the shuttle receptacle collects the extrudate. (B) After one empties, (C) the shuttle box fills it. (D–F) The cycle repeats itself for the second unit. (From Ref. 36.)

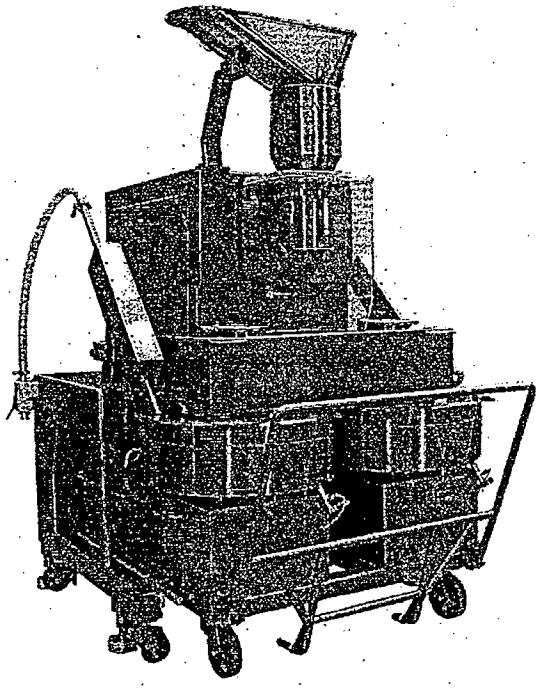


Figure 16 Twin spheronizer with extruder. (Courtesy of Niro Pharma Systems.)

has the potential to play a significant role in influencing the physical characteristics of the resulting product. Hasznos et al. (46) showed that a higher disk speed and longer residence time increased the coarse fraction and mean diameter and decreased the fine fraction. The faster speed and longer time also increased the moisture loss during the process. Since the moisture loss can reduce the plasticity of the particle, it can have the same effect as an underwet granulation. The particles may not round off into spheres and stay as deformed cylinders or dumbbells. Higher spheronizer

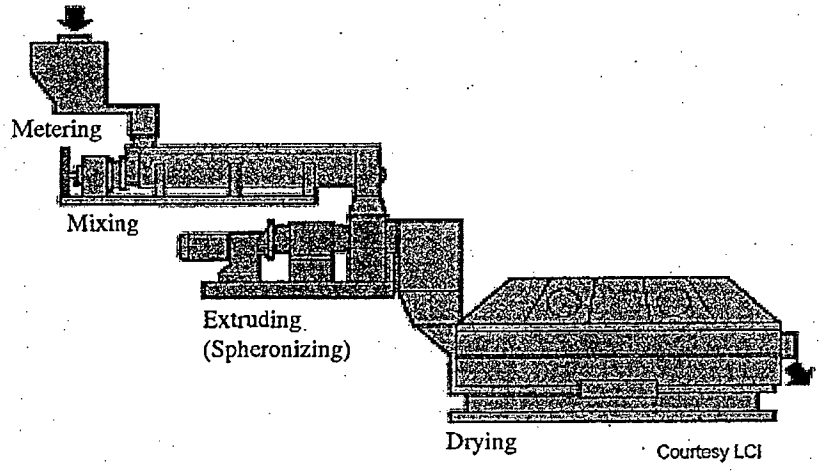


Figure 17 Typical semicontinuous pellet production setup. (Courtesy of LCI Corporation.)

charges reduced the moisture loss. They also suggested that an interaction between spheronizer speed and residence time indicated the total number of revolutions of the disk was critical. A change in one of the variables could be offset by an opposite change of the other, as long as the total number of revolutions remained constant (46). Hellén et al. showed a similar moisture loss during spheronization. In addition, they indicated that the major factors influencing the shape of the spheres were the disk speed and residence time. High speed and long time produced more spherical particles (26). Wan et al. indicated that a minimum disk speed and residence time was required to round the cylinder-shaped extrudate. Furthermore, an increase in speed or time, up to a limit, increased the median diameter of the spheres while higher speeds and longer times caused a reduction in size. Short residence times at high disk speeds resulted in small but round particles (50).

A number of investigators have reported the effect of disk speed and residence time on density. Woodruff and Neussle reported the variables to have no effect on the density of the spheres as compared to the density of the granulation and extrudate (16). These results are in conflict with most of the other studies; however, they are likely due to the use of mineral oil in the formulation. The oil can reduce the frictional forces at the die wall during extrusion and between particles and equipment surfaces during spheronization. A number of investigators including Malinowski and Smith reported that an increase in either disk speed or residence time resulted in an increase in density (20,21,26,47). Mehta et al. studied the effect of spheronization time on the pellet hardness and drug release (2). It was concluded that pellet hardness changed with spheronization time until about 10 min after which the hardness decreased until the 20 min point. No significant difference in pellet hardness from 20 to 40 min thereafter was observed. Mehta et al. explained this by the densification process occurring during the spheronization step. As spheronization time progresses from time zero to a certain time point "t" the extrudates are cut into uniform particles and shaped into spheres by the centrifugal and frictional forces present in the spheronizer during the operation. These forces act on each and every particle, making them denser and more spherical with time. However, after a critical period, no further densification occurs with an increase in spheronization time. In another study, Mehta et al. showed the effect of spheronization time on the porosity parameters of the pellets (51). It was summarized that a processing period of 2–10 min increased the number of pores and the total pore surface area and decreased the pore diameter. Beyond this time, for up to 20 min of spheronization time, the porosity was unchanged.

O'Connor et al. indicated that the friability of placebo spheres decreased with increasing residence time while the mean particle diameter decreased (24). Erkoboni et al. showed an increase in extruder screen size resulted in reduced friability (21).

4.5. Drying

Drying is the final step in the process. This can be accomplished in any dryer that can be used for conventional type granulations, including tray dryers, column type fluid beds, and deck type vibratory fluid beds. Each of the drying techniques has advantages; however, the major differences are based on the rate of water removal. Tray drying is the slowest of the processes. Fluidized bed dryers result in a much more rapid drying rate because of the higher air volumes and the potential use of higher inlet temperatures. Column fluid beds are batch dryers, while the deck type dryers offer the advantage of a continuous process. Both have been used successfully in

drying product produced by extrusion spheronization. The drying process must be chosen based on the desired particle properties. For example, pellets to be dried in fluid bed equipment will have to withstand fluidization process, resist attrition, and maintain its integrity.

Tray drying is a slow process in a static bed. Because of this, it can offer the greatest opportunity for a drug to migrate toward the surface and recrystallize (52). The more rapid rate in a fluid bed will likely minimize the effects of migration. This phenomenon can have an effect on a number of particle properties. The increased active concentration at the surface of the particle can increase the rate of dissolution. This recrystallization, however, can cause a problem for applications requiring film coating since the smooth surfaces developed by the spheronization process would be damaged. Additionally, the crushing strength of tray dried particles will likely be greater than their fluid bed counterparts. The slow recrystallization in the static bed allows for crystal bridges to develop as the fluid is removed and the solute recrystallizes.

5. FORMULATION VARIABLES

The composition of the wet mass is critical in determining the properties of the particles produced. This is clearly understood if we look at what material behaviors are required during each of the process steps. During the granulation step, a plastic mass is produced—a simple enough task if ended there. The materials must form a plastic mass, deform when extruded and break off to form uniformly sized cylindrical particles. A minimal amount of granulating fluid should migrate to the surface during extrusion and the particles should stay discrete during collection. During spheronization the particles must round off to form uniformly sized spheres. They must not dry out due to temperature or air volume or grow in size due to agglomeration. The fact is that a lot is expected from materials used in this process. This is especially true of formulations containing high percentages of active where low levels of excipients are used to impart the desired properties to the mass.

The importance of using sphere-forming excipients was noted early on. Conine and Hadley cited the necessity of using microcrystalline cellulose (4). Reynolds went on to indicate the need for either adhesive or capillary type binders (5). He cited cellulose gums, natural gums, and synthetic polymers as adhesives and microcrystalline cellulose, talc, and kaolin as capillary type binders. Since then much work has been conducted in an attempt to understand the significance of material properties. Some of the studies are discussed in the following text.

O'Connor et al. studied the behavior of some common excipients in extrusion/spheronization. The materials were studied as single components using water as the granulating fluid in an attempt to understand their application in the process. Of the materials tested, only MCC or MCC with Na-CMC (Na-caboxymethyl cellulose) was capable of being processed. Others including dicalcium phosphate, lactose, starch, and modified starch did not process adequately (24).

In an additional study, they investigated the effect of varying drug, excipient, and excipient:drug ratios. At low drug levels they found the spheronizing excipient played the most significant role in determining sphere properties. They found that, for low dose applications, MCC was the best excipient to use since it formed the most spherical particles. At moderate drug loading (50%), MCC as well as the two products consisting of MCC coprocessed with Na-CMC (Avicel® RC-581 and

Avicel CL-611) resulted in acceptable spheres. At higher loading levels, however, the MCC did not yield acceptable spheres and the coprocessed materials did. The spheres produced using Avicel CL-611 were the most spherical. In addition, they found dissolution to be dependent on the type of excipient used, the solubility, and concentration of the active. Spheres containing MCC remained intact and behaved as inert matrix systems, while those containing the coprocessed products formed a gel plug in the dissolution basket and were described as water-swellable hydrogel matrix systems. The release profiles for spheres containing each of the excipients and theophylline in a 50:50 ratio are shown in Figure 18.

Release profiles for spheres containing different drug loads are shown in Figure 19.

An increase in drug load resulted in an increased release rate. Release profiles for spheres containing actives having different solubilities, including chlorpheniramine maleate, quinidine sulfate, theophylline, and hydrochlorothiazide are shown in Figure 20. An increase in drug solubility resulted in an increased release rate (53).

Mehta and Kislalioglu demonstrated the use of polymethacrylate type polymers such as Eudragit L 100–55 and Eudragit S 100 via extrusion/spheronization in the development of controlled release pellets (13,54). They theorized that for the development of zero-order controlled release pellets of a poorly soluble drug, MCC would not be a good choice to form a pellet system via extrusion/spheronization. This would be due to the fact that MCC being insoluble would form a nondisintegrating matrix from which it would be difficult for an insoluble drug to be released. In their work they showed that Eudragit L100–55 and Eudragit S 100 can be used as pellet forming and release rate governing polymers for developing a controlled release drug delivery system with out the use of MCC in the matrix.

Zhou and Vervaet produced matrix pellets by combining microcrystalline waxes, pregelatinized starches, and hydrolyzed starches with model drugs such as Ibuprofen, chloroquin phosphate, and others (55). They concluded that the combination of microcrystalline waxes and pregelatinized starches or maltodextrins is a flexible system for the production of matrix pellets, even with a high drug concentration. Additionally, they concluded that the drug release with such a system could be

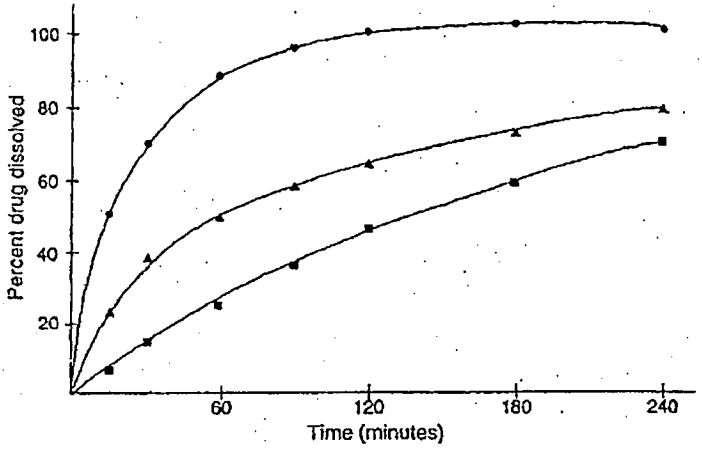


Figure 18 Dissolution profiles of spheres containing 50% theophylline in different Avicel MCC types • Avicel PH-101; ▲, Avicel RC-581; ■, Avicel CL-611. (From Ref. 53.)

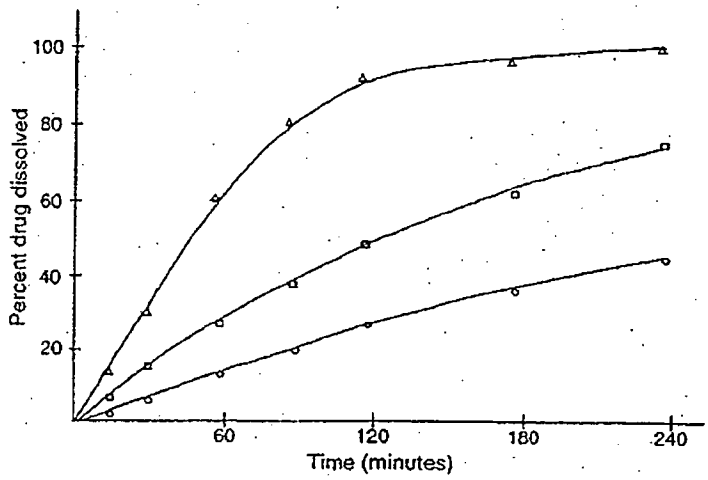


Figure 19 Dissolution profiles of spheres containing different concentrations of drug in Avicel CL-611: ○, 10%; □, 59%; △, 80%. (From Ref. 53.)

modeled by varying the type and the concentration of the wax and the starch. Tapia et al. described factors influencing the mechanism of release from sustained release matrix pellets, produced by the extrusion/spheronization process (56).

Kleinebudde and Jumaa concluded that during the extrusion process, water content in the extrudate and pellet porosity were increased as the degree of polymerization of MCC and powder cellulose in the matrix was increased (57).

Millili and Schwartz demonstrated the effect of granulating with water and ethanol at various ratios. The physical properties of the spheres changed significantly as the ratio of the two fluids was varied. Spheres could not be formed with absolute ethanol but were possible with 5:95 water:ethanol. An increase in the water fraction resulted in a decrease in porosity, friability, dissolution, and compressibility and an increase in density. The porosity of spheres granulated with 95% ethanol was 54%

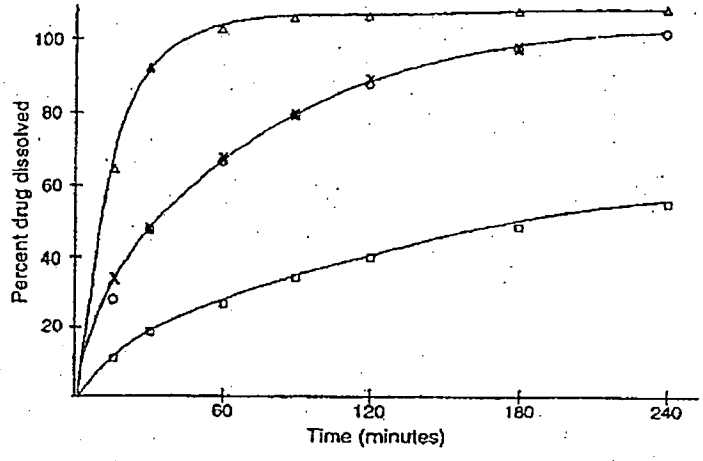


Figure 20 Dissolution profiles of spheres containing 10% drug in Avicel PH 101: •, chlorpheniramine maleate; ○, quinidine sulfate; ×, theophyline; □ hydrochlorothiazide. (From Ref. 53.)

while the water granulated product had a porosity of 14%. When greater than 30% water was used, spheres remained intact throughout the dissolution test. As previously discussed, water granulated spheres were very difficult to compress while spheres granulated with 95% ethanol were significantly more compressible than those prepared using water (18). In contrast, Mehta et al. showed that an increase in granulation water level increased the total number of pores in the pellet matrix without changing the pore diameters (51). Additionally they concluded that this direct increase in porosity increased the dissolution contact angle due to which dissolution of the poorly soluble drug was increased. Jerwanska et al. concluded that the rate of drug release increased with increased levels of granulation liquid because of a greater degree of porosity obtained after drying (58). They also correlated these results with differences in hardness of the pellets. This was similar to the findings by Mehta et al. Jerwanska et al. proposed that for a continuous extrusion process, adequate water is required to bridge the particles together until liquid saturation in the granulation is achieved. This strategy is necessary to deform the granulation to form extrudates and consequently shape them into spheres by spheronization. If the granulation water level is below the liquid saturation point, then the spheres obtained will be hard and less porous, thereby leading to decreased drug release rates. Above the liquid saturation point, the hardness and porosity of the pellets are not significantly decreased.

A tablet hardness vs. compression forces profile is shown in Figure 21.

In a later study, Millili et al. proposed a bonding mechanism, referred to as autohesion, to explain the differences in the properties of spheres granulated with water and ethanol. Autohesion is a term used to describe the strong bonds formed by the interdiffusion of free polymer chain ends across particle–particle interfaces (59).

Using a ram extruder, Harrison et al. demonstrated that steady state flow could not be achieved with lactose. Additionally, they demonstrated the reduced sensitivity of MCC to small changes in moisture as determined by the force required to induce plug flow in a cylinder. Comparing MCC to a MCC/lactose blend and 100% lactose,

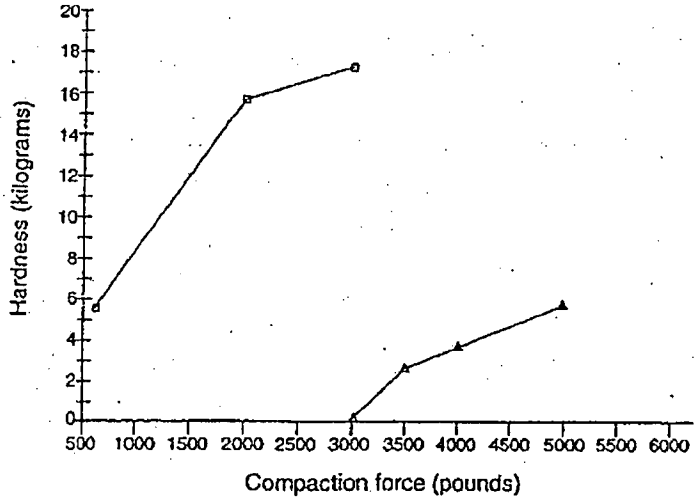


Figure 21 The effect of varying compression force on the hardness of compacted 16/30-mesh spheres of 10% theophylline–Avicel PH101: △, spheres prepared by water; □, spheres prepared by 95% ethanol granulation. (From Ref. 18.)

they found that, with lactose, small changes in moisture caused large changes in force while with MCC, larger changes in moisture were required to have similar effects on the force (29).

Baert et al. used mixtures of microcrystalline cellulose and coexcipients at various ratios to demonstrate the effect of solubility and the total fluid on extrusion forces. They showed that if the coexcipient was insoluble, such as dicalcium phosphate, the force required to extrude increased with increasing levels of coexcipient. When a soluble excipient such as lactose was used, the force required to extrude decreased with the addition of the initial amounts of lactose. After a certain level, however, the reduction in force stopped and began to increase. This was due to the initial solubilization of lactose and the resulting increase in the total fluid level. Once the fluid was saturated the remaining lactose was not soluble and the force began to increase. The increase began at about 10% lactose level for α-lactose and 20% for β-lactose. This was due to the difference in solubility between the two materials (33). The effects of dicalcium phosphate and various lactose grades on extrusion force are shown in Figure 22.

Funck et al. showed that low levels of common binders could be used to produce high drug loaded spheres with microcrystalline cellulose. Materials such as carbomer, Na-CMC, hydroxypropylcellulose (HPC), hydroxypropylmethylcellulose (HPMC), povidone (PVP), and pregelatinized starch were used. All materials were capable of producing spheres of acceptable quality. Dissolution testing showed spheres containing HPC and HPMC remained intact during testing while spheres containing starch, PVP, and Na-CMC disintegrated (60).

Lender and Kleinebudde reported that spheres produced with powdered cellulose had higher porosity and faster dissolution than those made using microcrystalline cellulose. Spheres could not be produced using only powdered cellulose and drug; a binder was required. The higher porosity of the spheres prepared from powdered cellulose may be beneficial for applications requiring compression (61).

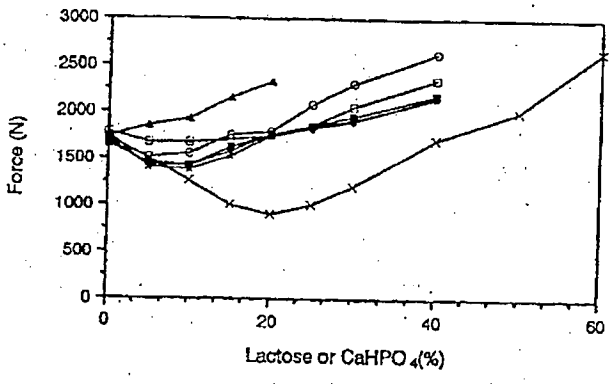


Figure 22 Influence of the amount of lactose or dicalcium phosphate dehydrate (% total weight) on the extrusion forces (N) for mixtures of lactose or dicalcium phosphate dehydrate–Avicel PH 101–water after granulation with a planetary mixer. Each end point is the mean of six values. The SD is lower than 3% for each point. Six different types of lactose were used: □, α-lactose monohydrate 80 mesh; ○, α-lactose monohydrate 200 mesh; •, α-lactose monohydrate 325 mesh; ■, spray dried lactose DCL 11; ×, anhydrous β-lactose DCL 21; ∗, anhydrous α-lactose DCL 30. One type of dicalcium phosphate dehydrate was used, ▲. (From Ref. 33.)

Feilden et al. showed that increasing the particle size of lactose resulted in forced flow and high extrusion forces, which resulted in poor quality extrudate and spheres having a wide size distribution. This was attributed to the increased pore diameter of the mixture containing the coarse lactose which allowed greater movement of water (62).

Chien and Nuessle (63) showed the use of a surfactant, such as sodium lauryl sulfate, reduced the migration of drug to the surface of the sphere during drying by reducing the surface tension of the granulating fluid. The reduction in surface tension also made it difficult to produce a cohesive extrudate in some cases.

Some miscellaneous observations include the following. Reynolds reported that excess extrudate friability can be overcome by incorporating more MCC, binder, or water in the granulation (5). Erkoboni et al. indicated that sphere hardness was most affected by the level of MCC in the formulation and the level of granulating fluid used (21). Hileman et al. showed that MCC had a narrower water range over which quality spheres could be made than MCC coprocessed Na-CMC (47). Hellén et al. showed that the surface characteristics were influenced by the water level with higher water levels giving smoother surfaces (26). Mehta et al. showed that when concentrations of pellet forming and release rate governing polymers in the matrix were changed, it altered the dissolution kinetics of a poorly soluble drug (2).

6. COMPRESSION OF PELLETS

Typically, pellets are produced for administering in a capsule dosage form after manufacturing with desired modified release properties. These pellets can be compressed into tablets as well. The tablets are normally intended to disintegrate into discrete pellets in the gastrointestinal tract and the drug should be subsequently be released in a controlled manner from the individual pellets. One challenge in the production of such tablets is maintaining the desired drug release after compaction, as the application of a compaction pressure can lead to structural changes in the film coating and consequently, altered drug release. Numerous investigations have been made into the compaction of pellets, coated or uncoated. It is imperative that the coated pellets do not lose their release properties during the compression stage. Pellets have been shown to react differently to compaction and consolidation than powders of the same material. Wang et al. reported compression of various lactose/microcrystalline cellulose compositions in powder or pellet form (64). Schwartz et al. (17) demonstrated the compaction characteristics of MCC processed into spheres are significantly different than the original powder. The powder material forms hard compacts at low compression forces, while the spheres are not compressible and form soft compacts, even at high forces. They indicated that spheres prepared from MCC showed a high degree of viscoelasticity over the entire compression range. Inclusion of coexcipients such as lactose and dicalcium phosphate increase the compactability by decreasing the viscoelastic resistance or pressure range over which the spheres behave elastically. A reduction in viscoelastic resistance was seen with spheres containing both lactose and dicalcium phosphate; however, dicalcium phosphate had a greater effect. Compaction profiles of spheres containing 10% theophylline with MCC, MCC/DCP, or MCC/lactose in a 22.5/67.5 ratio are shown in Figure 23.

A similar phenomenon was reported by Maganti and Celik when pellets produced by rotor granulation were compressed (65). They compared the compaction behavior of pellet formulations, mainly consisting of MCC, to that of the powders

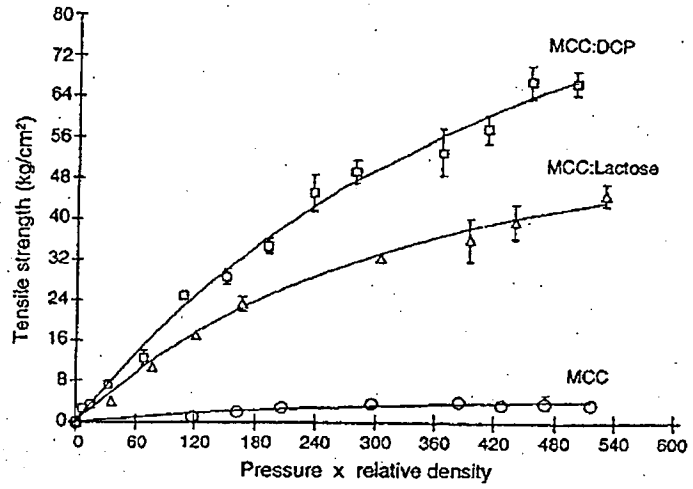


Figure 23 The effect of excipients on the compaction profile of spheres. Compaction profiles of spheres containing 10% theophylline with either MCC, MCC–DCP, or MCC–lactose in a 22.5:67.5 ratio using the Leunberger model. (From Ref. 17.)

from which they were formed and also found significant differences. The powders examined were found to compact by plastic deformation and produced strong compacts, while the pellets exhibited elastic deformation and brittle fragmentation, resulting in compacts of lower tensile strength. This can be explained by the fact that the pellets, which are large and spherical in shape as compared to the small, irregular powder particles they are composed of, have a low surface-to-volume ratio, which might result in a decreased area of contact between the particles as they consolidate. Nicklasson (66) investigated the compression behavior of pellets consisting of MCC, with or without other excipients such as polyethylene glycol and DCP. Deformation of the aggregates was found to depend on three deformation characteristics, namely, the capacity for, the mode of and the resistance to deformation. High surface deformation refers to the great ability of the pellets to conform to the surface of the surrounding pellets. In pellets containing the soft component, the primary particles can reposition within the agglomerate and the ability to fill the intragranular pore space is increased. For pellets containing hard materials, the compaction stress may give local failure at pellet surfaces. Thus, the material properties of the primary particles constituting the pellets are important for the compression behavior of pellets. In number of studies (67,68) various soft materials have been incorporated in pellets to modify their deformability and compatibility. Nicklasson and Alderborn (69) studied the modulation of the tableting behavior of pellets through the incorporation of polyethylene glycol and found that these soft pellets had an increased propensity to deform and altered mode of deformation to the relatively hard MCC pellets. Iloañusi et al. (67) found MCC-based bead formulations incorporating wax to be more compressible than those made without wax. Salako et al. (68) found that pellets containing theophylline and MCC were hard and less brittle than the ones containing glyceryl monostearate which were soft pellets. The soft pellets were found to fracture under low compression pressures and were able to form a coherent network of deformable material in the tablets at higher pressures. The hard pellets were unable

to form such a network at high pressures and found to reduce more in volume without bond formation than soft pellets.

The size of the pellets can also have a bearing on their compression behavior. Small pellets have been shown to be less affected than larger ones by the compaction process (70,71). Smaller beads were significantly stronger, relative to their size, than larger ones. Researchers also found that larger pellets were much more readily deformed (71). The application of coating to the pellet core can influence their compression characteristics. Magnati et al. (72) added a water-based ethyl cellulose coating (Surelease) to the MCC-based pellets previously used (65) and thereby altered their deformation characteristics, introducing plastoelastic properties whereas previously they had been brittle and elastic. The overall ability of the pellets to deform, both plastically and elastically, increased with an increasing coating level. Miller et al. (73) investigated the mechanical properties of tablets compressed from pellets coated with Surelease to that of uncoated pellets and found them to be comparable with the exception of the diametrical strain, which increased on coating. This was attributed to the flexibility of the plasticized ethyl cellulose, allowing greater deformation of the compact to occur before failure.

It has been found that coated pellets can be compressed into tablets while retaining controlled release of the drug, provided that the effect of excipients and compression force is considered and determined. The protective effect of an excipient is dependent on the particle size and the compaction characteristics of the material. In general, materials that deform plastically, such as MCC and PEG, give the best protective effect (74–77). Yuasa et al. studied the protective effect of 14 different excipients and were able to correlate the plastic energy percentage to the release rate, that is, materials that deform plastically were shown to protect the coating best (78). However, Stubberud et al. found that lactose, a fragmented material, gives better protection than MCC (79). The compressed induced changes in the structure of a film coating may depend on formulation factors, such as the type and the thickness of the coating, the properties and the structure of the substrate pellets, and the incorporation of excipient particles.

The optimum amount of excipients incorporated in the tablet formulation was concluded to be 30% (80). Palmieri et al. (81) showed that tablets consisting of maximum 40% coated granules had acceptable release profiles, using MCC as the tablet excipient. Wagner et al. (82) concluded that a tablet content of 70% (w/w) of pellets, approximately 1 mm diameter, is a critical level resulting in pronounced damage to the coating. On reducing the pellet proportion to 60% (w/w), tablets fulfilling the compendial dissolution requirements for enteric-coated products can be prepared. Tunón (83) investigated factors that influence the preparation of modified release pellets, its compression behavior, influence of inter- and intragranular factors and release of drug release of pellets. The most frequently encountered explanation for the loss of modified release upon compaction, in terms of an increased drug release rate, is the occurrence of cracks in the coating. However, knowledge of why and how cracks are formed in the coating and techniques to avoid them is highly valuable in the development of multiple unit tablets containing pellets.

7. CONCLUSIONS

Extrusion/spheronization is a versatile process capable of producing granules or spheres having unique physical properties. Since it may be more labor and time

intensive than the more common granulation techniques, it should be considered as a granulating technique when the desired properties cannot be produced using more conventional techniques. Potential applications are many including both immediate and controlled release. Regardless of the application, care must be taken to understand the desired properties and the formulation and process variables capable of achieving them. The use of statistical experimental design for formulation and process development is strongly recommended due to the high degree of interactions between the variables. Lastly, new technologies such as hot melt extrusion and spheronization (HME) are gaining considerable interest in the pharmaceutical drug delivery arena for solving specific problems such as enhancing taste masking, improving solubility and drug bioavailability and in general for controlled release drug delivery. Compression of pellets into modified release multiple unit dosage form is now possible once the proper understanding of the formulation of the core pellets, type of coating, and protective excipients to maintain the coating integrity of the pellets is understood.

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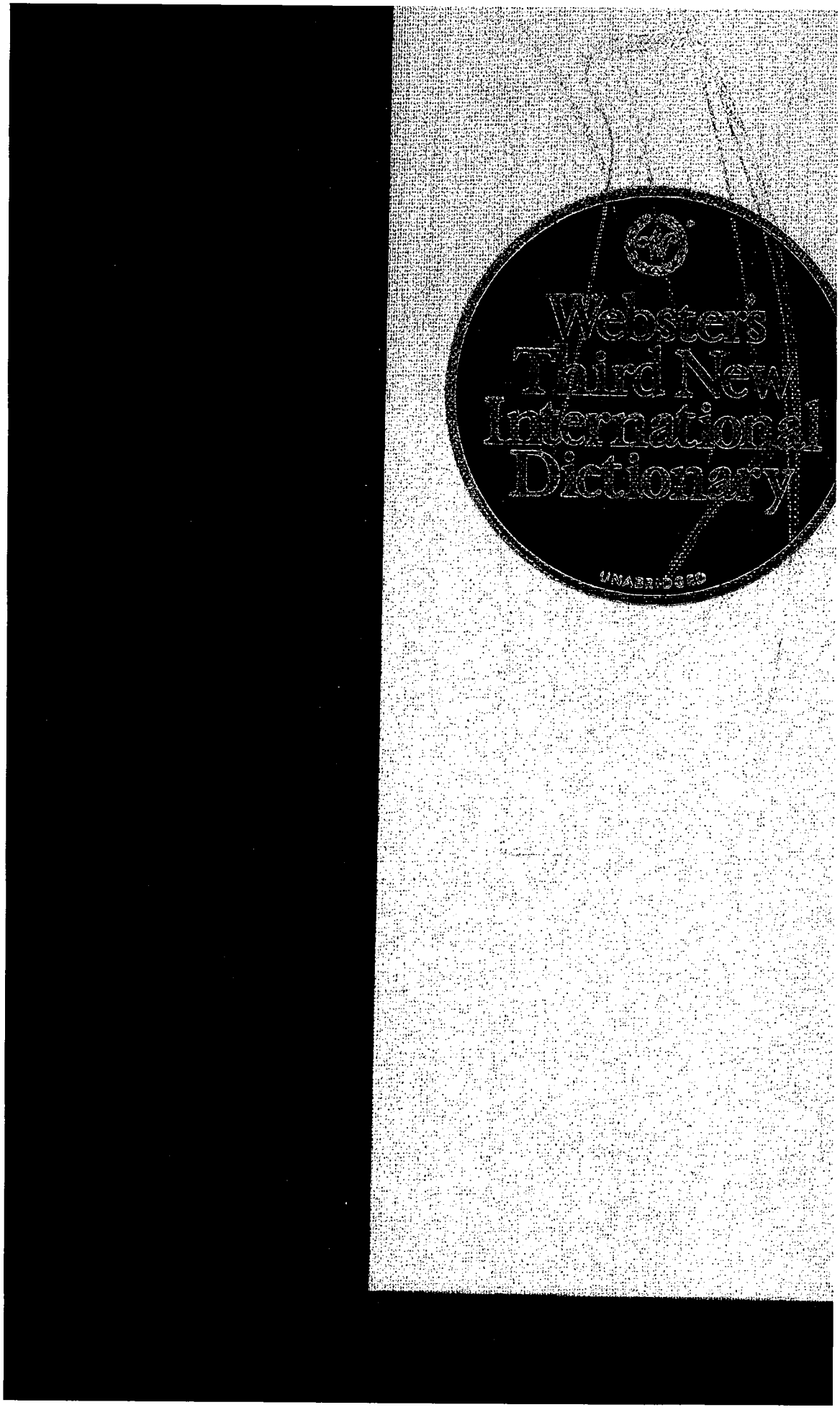
EXHIBIT O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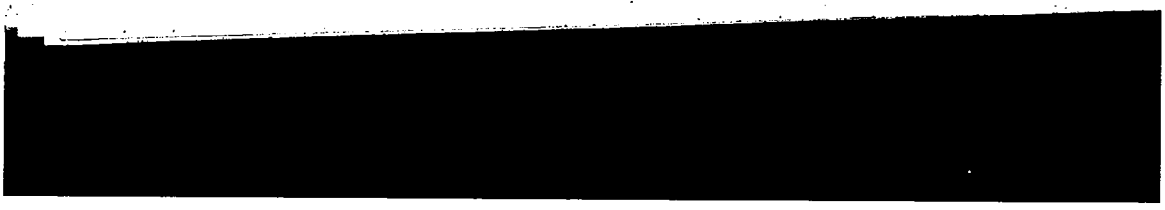

form critic *n* : a specialist in form criticism

form criticism *n* : a method of biblical criticism that seeks to classify units of scripture into literary patterns (as love poems, parables, sayings, elegies, legends) and that attempts to trace each type to its period of oral transmission in an effort to determine the original form and the relationship of the life and thought of the period to the development of the literary tradition

form cutter *n* : a cutting tool having its edge shaped to the profile to be imparted to the work

forme \'fō(ə)rm, -ȯ(ə)m\ *n* -s [F, lit., form — more at FORM] **1** *Brit* : ¹FORM 8 **2 a** : a pattern of an upper of a shoe **b** : a low bench on which shoemakers formerly sat when working

formed \'fō(ə)rmd, -ȯ(ə)md\ *adj* [ME, fr. past part. of *formen* to form — more at FORM] **1** : clearly defined : SETTLED, DEFINITE ⟨I have no ~ opinion about the chances of success⟩ **2** : fully developed (as by discipline or training) : MATURED ⟨a ~ opposition arose over the terms of the agreement⟩ ⟨a graceful but not yet fully ~ literary style⟩ **3** : being or having the characteristics of living matter : ORGANIZED ⟨~ ferments extracted from the gastric mucosa⟩ ⟨~ elements of the blood⟩ **4** : shaped (as by pressure or carving) to fit ⟨~ plastic snugly encloses the assembly⟩ ⟨a ~ handgrip on a grease gun⟩

formed coil *n* : an electric coil wound by a machine upon a form and transferred afterward to an armature as distinguished from a coil wound directly on the armature

for·me·don \'formə,dän\ *n* -s [ME, fr. AF, fr. ML *forma doni*, lit., form of a gift] : a former writ of right for recovering per formam doni entailed property under English law

for·mée *also* **for·mé** \'för,mā\ *or* **formy** \-,mē\ *adj* [ME *forme*, fr. MF *formé*, *fourmé*, past part. of *former*, *fourmer* to form — more at FORM] *of a cross* : having the arms narrow at the center and expanding toward the ends, the sides of the arms being either straight or concave lines and the ends of the arms cut off square or very slightly concave : PATTÉE — compare MALTESE CROSS 1; see CROSS illustration

forme fruste \fȯrmfrüst\ *n, pl* **formes frustes** \"\ [F, lit., worn-down form] : an atypical and usu. abortive manifestation of a disease

for·men·kreis \'fȯrmən,krīs\ *n, pl* **formenkrei·se** \-īzə\ *or* **formenkreis·es** \-īsəz\ [G, lit., cycle of forms, fr. *formen*, pl. of *form* (fr. MHG *forme*, fr. L *forma*) + *kreis* circle, cycle — more at FORM, ARTENKREIS] : a polytypic species (as of birds)

form·er \'fȯrmər, 'fō(ə)mə(r\ *n* -s [ME, fr. *formen* to form + *-er* — more at FORM] **1** : one that forms : MAKER, CREATOR, SHAPER ⟨discipline is a ~ of character⟩ **2** : a worker who forms materials into products or products from materials (as by cutting, pressing, bending, molding, or other hand or machine operation) — often used in combination with an attributive noun indicating the material acted on or the product produced ⟨a coil ~⟩ ⟨expert felt ~*s*⟩ **3** : a device, tool, or machine used to form some material or product: as **a** : a shape around or by which an article is to be shaped, molded, woven, wrapped, pasted, or otherwise constructed ⟨the ~ on which paper bags are pasted⟩ **b** : a templet, pattern, gauge, guide, or block by which an article is shaped or bent **c** : FORMING DIE **d** : a device or machine for bending sheet metal into various forms (as tubes or cylinders) **e** : a machine used in ropemaking for twisting yarn into strands **4** [¹*form* + *-er*] *chiefly Brit* : a member of a school form — usu. used in combination ⟨sixth *formers*⟩ ⟨invited the lower *formers* on a picnic⟩

²**for·mer** \"\ *adj* [ME, fr. *forme* first (fr. OE *forma*) + *-er* — more at FOREMOST] **1 a** : preceding in order of time; *usu* : of, relating to, or occurring in the past : ANTECEDENT, PREVIOUS, PRIOR, EARLIER ⟨recovered some of her ~ ease⟩ ⟨as we agreed in ~ correspondence⟩ **b** *obs* : being far distant in time : ANCIENT **2** : near the beginning : PRECEDING ⟨the ~ part of a discourse or argument⟩ **3** : first mentioned or in order of two things mentioned or understood ⟨of these two evils the ~ is the lesser⟩ **4** *obs* : anterior in place or situation : FRONT, FOREMOST **5** : having been at some previous time : ONETIME, SOMETIME ⟨~ president of his fraternity⟩ ⟨~ members of the legislature⟩

former adjudication *n* : RES JUDICATA

for·mer·et \'fȯrmə,ret\ *n* -s [F, fr. MF, fr. *forme* form, large window in a church — more at FORM] : a wall rib in a roof vaulted with ribs

former jeopardy *n* : JEOPARDY 3

for·mer·ly \'fȯrmə(r)lē, -ȯ(ə)məlē, -li\ *adv* [²*former* + *-ly*] **1** *obs* **a** : in time immediately preceding : just before **b** : BEFOREHAND, FIRST **2** : in time past : in the time of an earlier or previous period : ONCE, HERETOFORE, PREVIOUSLY ⟨~ there were giants in the world⟩ ⟨we ~ lived in the country⟩ ⟨a ~ prosperous area⟩

for·mes \'fȯr,mēz\ *n pl comb form* [NL, fr. L, pl. of *-formis* -form] : ones having (such a) form : ones resembling — in names of zoological orders and certain other groups of higher rank than family ⟨Galli*formes*⟩ ⟨Passeri*formes*⟩

form factor *n* : the ratio between the volume of a tree and that of a geometric solid (as a cylinder) having the same diameter and height

formfitting \'·;··\ *adj* : conforming to the outline of the body : CLOSE-FITTING ⟨a ~ sweater⟩ ⟨a comfortably ~ armchair⟩

form·ful \'·fəl\ *adj* : exhibiting or notable for form (as in a sport) ⟨a ~ jump —*Time*⟩

form genus *n* : an artificial taxonomic category established for organisms of which the true relationships are obscure due to incomplete knowledge of structure (as in some fossils) or of development or life history (as in Fungi Imperfecti and various animal parasites)

form grinder *n* : a grinding wheel shaped to the contour to be imparted to the work — compare FORM CUTTER

for·mic \'fȯrmik, -ōəm-\ *adj* [irreg. fr. L *formica* ant — more at PISMIRE] **1** : of or relating to ants **2** : being or derived from formic acid

For·mi·ca \fȯr'mīkə\ *n, cap* [NL, fr. L, ant] : a genus of hymenopterous insects formerly including all the ants but now restricted to various typical ants (as the mound-building ants and the sanguinary ant)

For·mi·ca \(')fȯr;mīkə, fər'm-\ *trademark* — used for various laminated plastic products used esp. in furniture (as for tabletops) and in building (as for wallboards)

formic acid *n* : a colorless pungent fuming vesicatory liquid acid $HCOOH$ that occurs naturally in most ants and some other insects and in many plants, that is usu. made by acidification of sodium formate, and that is used chiefly in dyeing and finishing textiles as an acidifying or reducing agent — called also *methanoic acid*

formic aldehyde *n* : FORMALDEHYDE

for·mi·can \fȯr'mīkən\ *adj* [L *formica* + E *-an*] : of or relating to ants

For·mi·ca·ri·idae \,fȯrməkə'rīə,dē\ *n pl, cap* [NL, fr. *Formicarius*, type genus (fr. L *formica* + *-arius* -ary) + *-idae*] : a large family (suborder Tyranni) comprising the typical antbirds of tropical America — compare FURNARIIDAE — **for·mi·car·i·oid** \-'ka(a)rē,ȯid\ *adj or n* — **for·mi·car·oid** \-'ka(a),rȯid\ *adj*

for·mi·car·i·um \-'kerēəm, -'a(a)r-, -'ār-\ *n, pl* **formicar·ia** \-rēə\ [ML] : FORMICARY; *specif* : an artificial ant nest arranged for observation or study of the activities of the insects

for·mi·cary \'fȯrmə,kerē, -i\ *n* -ES [ML *formicarium*, fr. L *formica* ant + *-arium* -ary] : the dwelling of a colony of ants : an ant hill or ant nest

for·mi·ca·tion \,··'kāshən\ *n* -s [L *formication-*, *formicatio*, fr. *formicatus* (past part. of *formicare* to crawl like an ant, fr. *formica* ant) + *-ion-*, *-io* -ion — more at PISMIRE] : an abnormal sensation resembling that made by insects creeping in or on the skin

For·mic·i·dae \fȯr'misə,dē\ *n pl, cap* [NL, fr. *Formica*, type genus + *-idae*] : a family of hymenopterous insects including all the ants

for·mi·cide \'fȯrmə,sīd\ *n* -s [L *formica* ant + E *-cide*] : a substance used for destroying ants

¹**for·mi·cine** \-,sīn, -,sən\ *adj* [L *formicinus*, fr. *formica* ant + *-inus* -ine] **1** : of, relating to, or resembling an ant **2** [NL *Formicinae* group of ants, fr. L, fem. pl. of *formicinus*] : belonging to a group of ants that resemble and are closely related to those of the genus *Formica*

²**formicine** \"\ *n* -s : a formicine ant

for·mi·civ·o·rous \;··;siv(ə)rəs\ *adj* [L *formica* ant + E *-i-* + *-vorous*] : feeding on ants

For·mi·coi·dea \,··'kȯidēə\ *n pl, cap* [NL, fr. *Formica* + *-oidea*] : a superfamily of aculeate hymenopterous insects consisting of the ants and being coextensive with Formicidae

for·mi·col·o·gist \-'käləjəst\ *n* -s [L *formica* ant + E *-o-* + *-logist*] : MYRMECOLOGIST

for·mi·da·bil·i·ty \,fō(r)mədə'biləd·ē, -ətē, -i\ *n* -ES : formidable quality ⟨a ~, in both size and substance, which must have deterred many readers —*Times Lit. Supp.*⟩

for·mi·da·ble \'fō(r)mədəbəl, fō(r)'mid-\ *adj* [ME, fr. L *formidabilis*, fr. *formidare* to fear, dread (fr. *formido* fear, terror) + *-abilis* -able; akin to Gk *mormō* she-monster, bugbear, *mormoros* fear] **1** : exciting fear, dread, or apprehension ⟨a grim and ~ foe⟩ ⟨a ~ prospect⟩ ⟨the first attack was dangerous, but a second must be more ~ still —William Cowper⟩ **2** : able seriously to impede a projected interaction or course of action usu. by interposing difficulties, hardships, or obstructions ⟨the mountains were a ~ barrier to our progress⟩ ⟨these qualities . . . made the Miltonic sentence a ~ construction —R.M.Weaver⟩; *broadly* : DIFFICULT ⟨~ coloratura passages⟩ **3** : tending to inspire awe or wonder usu. by reason of notable size, quantity, superiority, or excellence ⟨had a ~ array of compositions to his credit —Joseph Wechsberg⟩; *broadly* : LARGE, SUPERIOR, OUTSTANDING ⟨in a society based on oral tradition the memory of the elders is ~⟩ ⟨a social lioness of ~ glamour⟩ ⟨his ~ accomplishments in art⟩ — **for·mi·da·ble·ness** \-nəs\ *n* -ES — **for·mi·da·bly** \-əblē, -li\ *adv*

forming *pres part of* FORM

forming die *n* : a die resembling a drawing die but lacking a blank holder

forming press *n* : a punch press used for forming (as metal parts)

forming punch *n* : a punch that operates with a forming die

forming rolls *n pl* : a set of rolls shaped to give a predetermined contour of cross section to work run through them

forming tool *n* **1** *or* **form tool** : a tool or machine accessory so shaped that it imparts a predetermined contour or profile to the work **2** : a pair of light tongs with broad flat ends used in manipulating and shaping softened glass

form·ism \'fō(r),mizəm\ *n* -s [¹*form* + *-ism*] : a philosophical theory (as Platonism or Aristotelianism) assigning a preeminent place to metaphysical forms

form·ist \-,məst\ *n* -s : one who advocates strict adherence to forms — **form·is·tic** \(,)·'mistik\ *adj*

form·less \'·ləs\ *adj* : deficient in or lacking form: as **a** : having no regular or inherent shape ⟨fluids are ~, taking the shape of their container⟩ **b** : SHAPELESS 2 ⟨a ~ old dress⟩ **c** : lacking order or arrangement : INCHOATE ⟨the ~ welter of his prose works —George Saintsbury⟩ **d** : having no physical existence : IMMATERIAL ⟨the primitive society exists in a world filled with taboos, mysteries, and ~ but often malevolent beings⟩ — **form·less·ly** *adv* — **form·less·ness** *n* -ES

form letter *n* : a letter on a subject of frequent recurrence (as in a business house) that can be sent to different persons without essential change other than in the address

form line *n* : a line drawn on a map to depict surface configuration in a generalized manner and usu. without indicating elevations — compare CONTOUR LINE

form master *n* : a teacher in charge of a form esp. in an English secondary school

formo- — see FORM-

form of action : one of the personal actions formerly brought at common law (as assumpsit, detinue, replevin)

form of address : a formula generally accepted as proper or suitable for addressing an individual of a particular rank or status either orally or in writing

form of discourse : one of the types into which discourses are classified according to function and which comprise exposition, argument, description, and narration

form of forms : FIRST CAUSE

form oil *n* : oil with which concrete forms esp. of metal are sometimes treated to prevent sticking upon removal

For·mol \'fȯr,mōl, -ōl\ *trademark* — used for an aqueous solution of formaldehyde

for·mol·ize \-,līz\ *vt* -ED/-ING/-S *see -ize in Explan Notes* [*Formol* + *-ize*] : to treat (as a serum) with a dilute formaldehyde solution esp. for the purpose of attenuating a virus or toxin

for·mo·nitrile \fȯr,mō+\ *n* -s [ISV *form-* + *nitrile*] : HYDROGEN CYANIDE

for·mo·sa \fō(r)'mōsə, -zə\ *adj, usu cap* [fr. *Formosa*, island in the China Sea] : of or from the island of Formosa ⟨*Formosa* tea⟩ : of the kind or style prevalent in Formosa : FORMOSAN

formosa camphor *n, usu cap F* : dextrorotatory camphor

¹**for·mo·san** \-s'n, -z'n\ *adj, usu cap* [*Formosa* + E *-an*] **1** : of or relating to the island of Formosa or its inhabitants **2** : of, relating to, or in the Formosan language

²**formosan** \"\ *n* -s *cap* **1 a** : a native or inhabitant of Formosa **b** : a member of one of the largely uncivilized groups of mixed Mongolian and Indonesian descent that live in the interior of the island **2 a** : the Indonesian languages of the Formosan people **b** : any of these languages

formosan pheasant *n, usu cap F* : a rather light-colored pheasant native to Formosa that is probably a variety of the ring-necked pheasant with which it freely interbreeds and that like the latter has been widely introduced in No. America

for·mos·i·ty \fȯr'mäsəd·ē, -ətē, -i\ *n* -ES [ME *formosite*, fr. L *formositas*, fr. *formosus* beautiful (fr. *forma* form, beauty + *-osus* -ous) + *-itas* -ity — more at FORM] *archaic* : beauty or a beautiful thing

form quotient *n* : the ratio of the breast-high diameter of a tree to the diameter at some higher point

forms *pl of* FORM, *pres 3d sing of* FORM

form species *n* : a taxonomic species placed in a form genus

for·mu·la \'fȯrmyələ, -ō(ə)m-\ *n, pl* **formu·las** \-ləz\ *also* **formu·lae** \-,lē, -,lī\ *often attrib* [L, dim. of *forma* form] **1 a** : a set form of words for use in a ceremony or ritual **b** : a formal statement of religious doctrine or a written confession of faith **c** : a conventionalized statement intended to express some fundamental truth or principle esp. as a basis for negotiation, discussion, or action ⟨the two nations sought a ~ that would allow settling of the border dispute⟩ ⟨the ~ "54–40 or fight"⟩ **2 a** : a recipe or prescription giving method and proportions of ingredients for the preparation of some material (as a medicine, a blend of coffee, or a caulking compound) **b** : a milk mixture or substitute for feeding an infant typically consisting of prescribed proportions and forms of cow's milk, water, and sugar; *often* : a batch of this made up at one time to meet an infant's future requirements (as during a 24-hour period) **3 a** : a general fact, rule, or principle expressed in symbols ⟨certain earlier workers attempted to differentiate nematodes by a ~ of numerical ratios⟩ **b** : a symbolic expression showing the composition or constitution of a chemical substance and consisting of symbols for the elements present and subscripts to indicate the relative or total number of atoms present in a molecule ⟨the ~*s* for water, sulfuric acid, and ethyl alcohol are H_2O, H_2SO_4, and C_2H_5OH respectively⟩ — *see* EMPIRICAL FORMULA, GENERAL FORMULA, MOLECULAR FORMULA, STRUCTURAL FORMULA **c** : a group of symbols (as numbers, letters, or arbitrary signs) associated to express briefly a single concept; *also, in logic* : any combination of signs in an uninterpreted calculus **d** *in logic* : an expression (as a statement or matrix) stipulated to be meaningful by the rules of the calculus to which it belongs; *esp* : such an expression containing only variables **4** : a prescribed or set form : a fixed or conventional method (as of acting, arranging, or speaking) : an established rule or custom — often used somewhat derogatorily ⟨many of the paintings were unimaginative ~ works⟩ ⟨the limitations of ~ fiction —Coleman Rosenberger⟩ **5** : any of the various written forms by which the praetors of ancient Rome referred causes to judges or arbitrators for hearing and adjudication upon a summons of the defendant into court by the plaintiff

for·mu·lable \-ləbəl\ *adj* [*formulate* + *-able*] : capable of being formulated

for·mu·la·ic \;··;lā·ik\ *adj* [*formula* + *-ic*] : characterized by or made up of formulas : constituting a formula ⟨~ expression of ideas⟩ ⟨a ~ phrase⟩ — **for·mu·la·i·cal·ly** \-ək(ə)lē\ *adv*

for·mu·lar·ism \'fȯrmyələ,rizəm\ *n* -s [¹*formulary* + *-ism*] : the practice of depending on or adhering strictly to set formulas — **for·mu·lar·is·tic** \;···;ristik\ *adj*

for·mu·la·ri·zable \;···;rīzəbəl\ *adj* : capable of being reduced to a formula : FORMULABLE

for·mu·lar·iza·tion \,····rə'zāshən, -,rī'z-\ *n* -s : an act or a product of formularizing

for·mu·lar·ize \-,rīz\ *vt* -ED/-ING/-S [¹*formulary* + *-ize*] **1** : to state in or reduce to a formula : FORMULATE **2** : to bind or circumscribe the action of by formulas ⟨men tricked by their own ingenuity into becoming *formularized* slaves of the machines they created⟩ — **for·mu·lar·iz·er** \-zə(r\ *n* -s

¹**for·mu·lary** \'··,lerē, -ri\ *n* -ES [MF *formulaire*, fr. *formule* formula (fr. L *formula*) + *-aire* -ary] **1** : a book or other collection of stated and prescribed forms (as of oaths, declarations, or prayers) : a system of formulas ⟨a liturgical ~⟩ **2** : a prescribed form or model : FORMULA **3** : a book containing a list of medicinal substances and formulas for making medicines

²**formulary** \"\ *adj* [*formula* + *-ary*] **1** : of or relating to formulas or to a formulary system **2** : constituting a formula ⟨a ~ solution of a problem⟩ **3** : preoccupied with or adhering to formulas ⟨a stiff ~ man⟩

formulas *pl of* FORMULA

for·mu·lat·able \'··,lād·əbəl\ *adj* : capable of being formulated

for·mu·late \-,lāt, *usu* -ād·+V\ *vt* -ED/-ING/-S [*formula* + *-ate*] **1 a** : to reduce to or express in or as if in a formula : put into a systematized statement or expression **b** : to plan out in orderly fashion : DEVISE ⟨*formulating* expedients to meet the emergency⟩ **2 a** : to develop a formula for the preparation of (as a soap or a plastic) : standardize by formula **b** : to make or prepare in accord with a formula

for·mu·la·tion \,··'lāshən\ *n* -s : an act or the product of formulating ⟨his ~ of the data was clear and concise⟩ ⟨a new varnish ~⟩

for·mu·la·tive \'··,lād·iv, -ātiv, -ēv\ *adj* : tending to effect formulation ⟨exerting ~ influences on the student's thought processes⟩

for·mu·la·tor \-,lād·ə(r), -āta-\ *n* -s : one that formulates; *esp* : a developer of commercial and industrial formulas

for·mu·la·to·ry \-lə,tōrē, -,ȯr-\ *adj* : of or relating to formulation

for·mule \'fȯr(,)myül\ *n* -s [F, fr. L *formula* — more at FORMULA] : FORMULA

for·mu·lism \-,myə,lizəm\ *n* -s [*formula* + *-ism*] : attachment to or reliance on formulas

for·mu·lis·tic \;··;listik\ *adj* : based on or characterized by a formula

for·mu·li·za·tion \,··lə'zāshən, -,lī'z-\ *n* -s : FORMULATION

for·mu·lize \'··,līz\ *vt* -ED/-ING/-S [*formula* + *-ize*] : FORMULATE 1

form up *vi* : to assume or participate in an orderly arrangement ⟨the waiting crowd *formed up* in a long line⟩ ⟨the planes *formed up* over the airfield⟩

Form·var \'fȯrm,vär\ *trademark* — used for various thermoplastic resins that are formals of polyvinyl alcohol and are used esp. in coatings, adhesives, and molding materials

form word *n* : FUNCTION WORD

formwork \'·,·\ *n* : a set of forms in place for the reception of concrete

formy *var of* FORMÉE

for·myl \'fȯr,mil, -,məl\ *n* -s [ISV *form-* + *-yl*] : the radical HCO– of formic acid that is also characteristic of aldehydes

for·myl·ate \-,mə,lāt\ *vt* -ED/-ING/-S [*formyl* + *-ate*] : to introduce formyl into (a compound) — **for·myl·a·tion** \,··'lāshən\ *n* -s

formyl violet S4B *n, usu cap F&V* : an acid dye — see DYE table I (under *Acid Violet 17*)

for·nent \fə(r)'nent\ *or* **for·ninst** \-'ninzt, -'nin(t)st\ *also* **for·nenst** \-'nenzt, -'nen(t)st\ *prep* [ME (Sc dial.) *fornent*, *forenent*, *fornentis*, fr. ME *for-*, *fore-* fore + *anent* or *anentes* anenst — more at ANENT, ANENST] **1** *dial* : in front of : OPPOSITE ⟨a little square ~ the church⟩ **2** *dial* : near to : alongside of : BESIDE, AGAINST ⟨left the shovel ~ the fence⟩

¹**for·ni·cate** \'fō(r)nə,kāt, *usu* -ād·+V\ *vb* -ED/-ING/-S [LL *fornicatus*, past part. of *fornicare*, *fornicari*, fr. L *fornic-*, *fornix* arch, vault, arched basement (inhabited by people of the lower classes), brothel, prob. fr. *fornus*, *furnus* oven — more at FURNACE] *vi* : to commit fornication ~ *vt* : to engage in fornication with

²**for·ni·cate** \-nəkət, -nə,kāt\ *also* **for·ni·cat·ed** \-nə,kād·əd\ *adj* [L *fornicatus*, fr. *fornic-*, *fornix* arch, vault + L *-atus* -ate, -ated] **1** : having an arched or vaulted form ⟨a small mollusk with an abruptly ~ shell⟩ ⟨broad ~ leaves⟩ **2** *of plants* : having fornices

¹**for·ni·ca·tion** \,fō(r)nə'kāshən\ *n* -s [ME *fornicacioun*, fr. MF & LL; MF *fornication*, fr. LL *fornication-*, *fornicatio*, fr. *fornicatus* (past part.) + L *-ion-*, *-io* -ion] **1** : human sexual intercourse other than between a man and his wife : sexual intercourse between a spouse and an unmarried person : sexual intercourse between unmarried people — used in some translations (as AV, DV) of the Bible (as in Mt 5:32) for *unchastity* (as in RSV) or *immorality* (as in NCE) to cover all sexual intercourse except between husband and wife or concubine **2** : sexual intercourse on the part of an unmarried person accomplished with consent and not deemed adultery — compare INCEST, RAPE

²**fornication** \"\ *n* -s [L *fornication-*, *fornicatio*, fr. *fornicatus* vaulted + *-ion-*, *-io* -ion] : a vaulting or arching : vaulted construction (as of a cloister)

for·ni·ca·tor \'fō(r)nə,kād·ə(r), -āta-\ *n* -s [ME *fornicatour*, fr. LL *fornicator*, fr. *fornicatus* (past part.) + L *-or*] : a person guilty of fornication — sometimes used to distinguish the male participant in such conduct; compare FORNICATRIX

for·ni·ca·to·ry \'fō(r)nəkə,tōrē, fō(r)'nik-\ *adj* [*fornicate* + *-ory*] : of or relating to fornication ⟨~ literature⟩

fornicatress *n* -ES [*fornicator* + *-ess*] *obs* : FORNICATRIX

for·ni·ca·trix \,fō(r)nə'kā·triks\ *n, pl* **fornicatri·ces** \-kə'trī,sēz\ [LL, fem. of *fornicator*] : a woman guilty of fornication — compare FORNICATOR

for·nic·i·form \(')fȯr;nisə,fȯrm\ *adj* [L *fornic-*, *fornix* + E *-iform*] : FORNICATE

for·nix \'fȯrniks, -nēks\ *n, pl* **forni·ces** \-nə,sēz\ [NL, fr. L, arch, vault — more at FORNICATE] **1** *anat* : an arch or fold of an arched or folded structure: as **a** : the vault of the cranium **b** : the part of the conjunctiva overlying the cornea **c** : a body of nerve fibers lying beneath the corpus callosum with which they are continuous posteriorly and serving to integrate the hippocampus with other parts of the brain **d** : the vaulted upper part of the vagina surrounding the uterine cervix **e** : the fundus of the stomach **f** : the vault of the pharynx **2** : one of the small arched scales in the throat of the corolla of some plants (as members of the genus *Myosotis*)

for·pine \fə(r)'pīn\ *vb* -ED/-ING/-S [ME *forpinen*, fr. *for-* + *pinen* to pine — more at PINE] *archaic* : to waste or pine away (as from anguish or suffering)

for·pit *or* **for·pet** \'fōrpət\ *n* -s [alter. of *fourth part*] *chiefly Scot* : ¼ peck

for·rad *or* **for·rard** \'fōrə(r)d\ *dial var of* FORWARD

for·rad·er *also* **for·rard·er** \-də(r)\ *chiefly dial comparative of* FORWARD

for real *adv* **1** : in earnest : SERIOUSLY ⟨this was no casual scuffling: they were fighting *for real*⟩ **2** *slang* : REALLY ⟨now you've messed things up *for real*⟩

forrel *var of* FOREL

for·rit \'fōrət\ *chiefly Scot var of* FORWARD

for·rit·some \-tsəm\ *adj* [*forrit* + *-some*] *Scot* : BOLD, IMPUDENT, FORWARD

fors *pl of* FOR

for·sake \fə(r)'sāk, fȯr'-, fō(ə)'-\ *vt* **for·sook** \-'sůk\ **for·saken** \-'sākən\ **forsaking**; **forsakes** [ME *forsaken* to reject, forsake, fr. OE *forsacan*, fr. *for-* + *sacan* to dispute; Goth *sakan* to quarrel — more at SAKE] **1** : to renounce or surrender (as a custom or practice formerly held dear) ⟨promised to ~ his bad habits if she would marry him⟩ **2** : to quit or leave entirely : depart or withdraw from : LEAVE, DESERT, ABANDON ⟨false friends ~ us in adversity⟩ ⟨*forsook* the theater for a career in politics⟩

forsaken *adj* [ME, fr. past part. of *forsaken*] : left desolate or empty : DESERTED ⟨the ~ slopes where children once played on

EXHIBIT P

ENTIRE EXHIBIT REDACTED

CERTIFICATE OF SERVICE

I hereby certify that on this 15th day of May, 2007, I electronically filed the foregoing document, **REDACTED VERSION OF DECLARATION OF MARY B. MATTERER IN SUPPORT OF DEFENDANT'S OPENING CLAIM CONSTRUCTION BRIEF,** with the Clerk of the Court using CM/ECF which sent notification of such filing to the following:

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Additionally, I hereby certify that the foregoing document was served as indicated below:

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